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DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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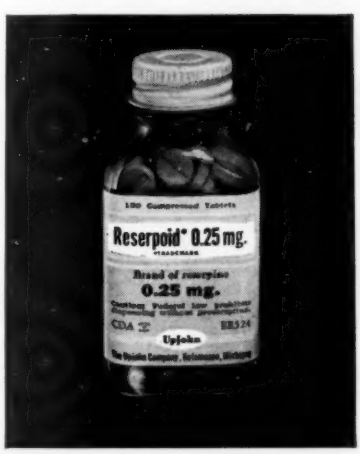

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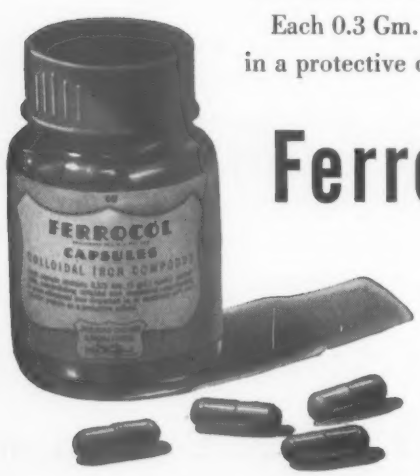

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1. Fowler, W. M.: Current Therapy for 1951, Saunders.
2. Creskoff, A. J.: Am. J. Med. Sci., November, 1950.
3. Fowler, W. M. and Barer, A., Am. J. Med. Sci., June, 1952.

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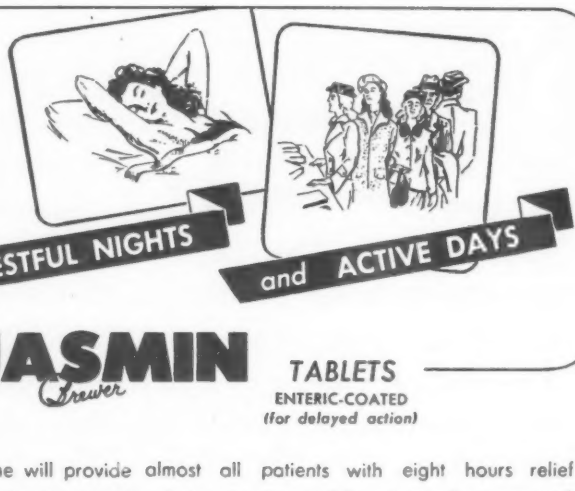

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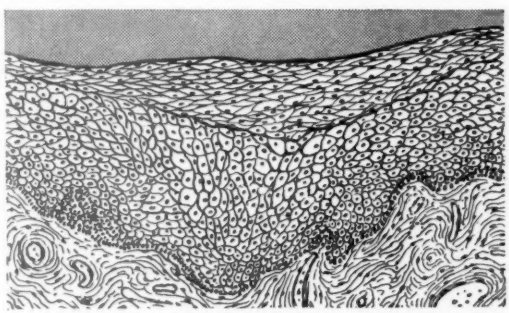
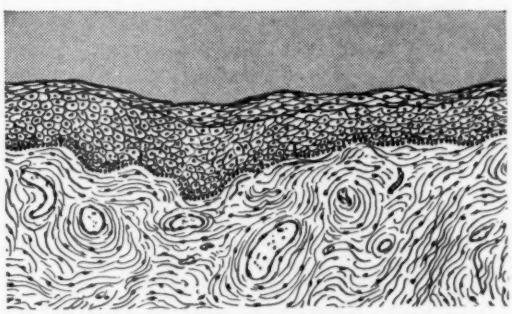
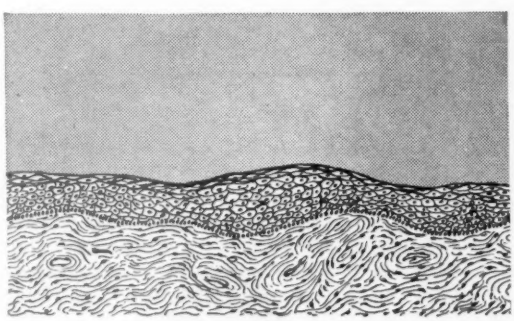


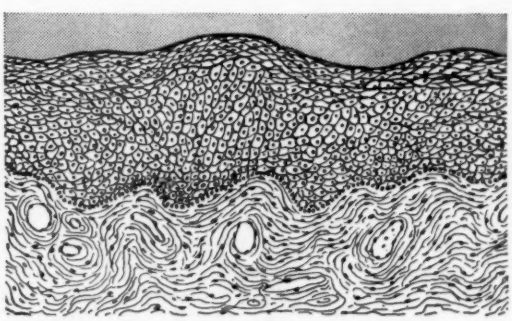
Adult vaginal epithelium maintained by estrogen activity.



During menopause, mucosa reverts to the infantile type.



Postmenopausal mucosa—thinning and atrophy of layers.



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*Sturnick, M. I., and Gargill, S. L.: New England J. Med. *247*:829 (Nov. 27) 1952.

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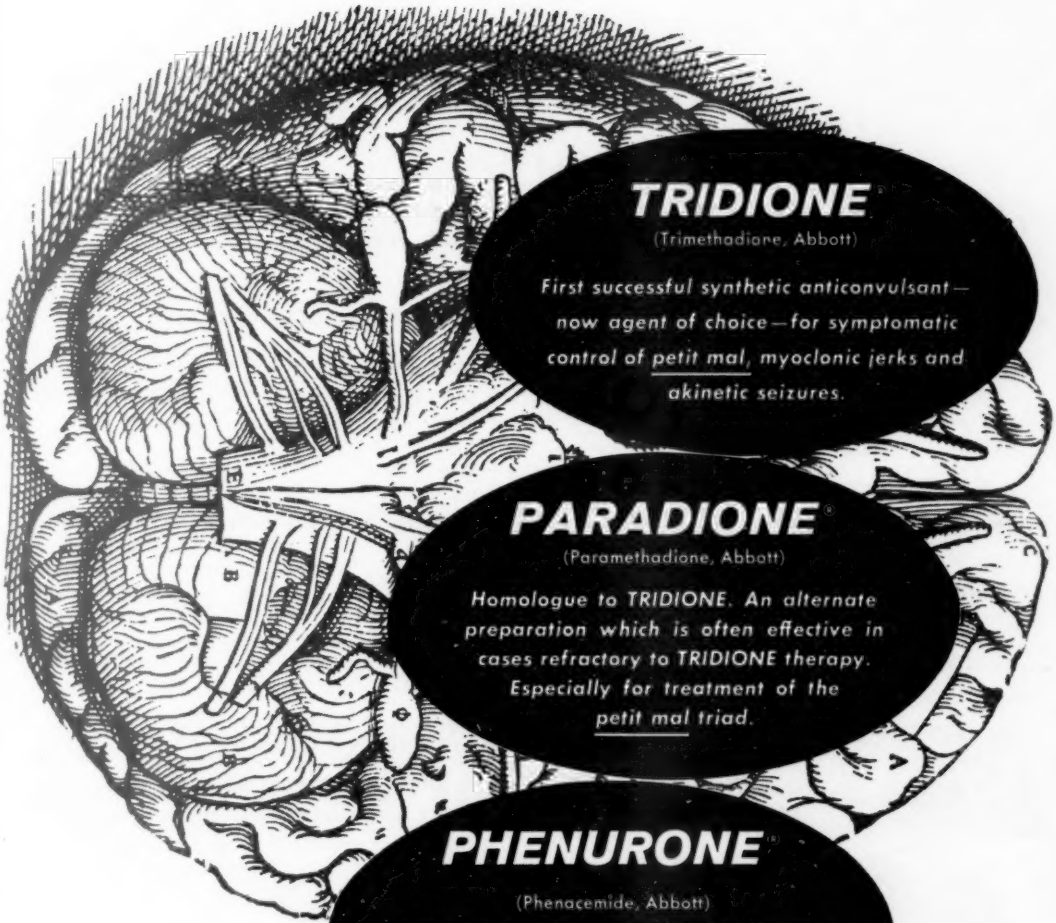

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JUNE, 1955

ORIGINAL ARTICLES

EVALUATION OF 1954 FIELD TRIAL OF POLIOMYELITIS VACCINE: SYNOPSIS OF SUMMARY REPORT*

By Thomas Francis, Jr., M.D.
DIRECTOR, POLIOMYELITIS VACCINE EVALUATION CENTER, UNIVERSITY OF MICHIGAN

AND

Robert F. Korns, M.D.
DEPUTY DIRECTOR, POLIOMYELITIS VACCINE EVALUATION CENTER, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN

During the spring of 1954 an extensive Field Trial of the prophylactic effectiveness of formalin-inactivated poliomylelitis vaccine, as developed by Dr. Jonas Salk and his associates, was initiated by the National Foundation for Infantile Paralysis.

The Poliomyelitis Vaccine Evaluation Center was established at the University of Michigan for the purpose of impartially collating and analyzing data collected through the combined efforts of many thousands of health department workers, practicing physicians, physical therapists and laboratory people scattered through the 211 participating study areas in 44 states.

The study design was dictated by both scientific and practical considerations, necessary in a project of such scope and dependent on the good will and abilities of so many people of varying capacity. They involved the organization and execution of the vaccination clinic program, the maintenance of detailed and accurate records, as well as the thorough investigation, according to a detailed plan, of each reported case of poliomyelitis in the area. Originally, it was deemed impractical to establish a strict placebo control experiment, with the complex administrative problem of giving three injections in sequence to each child, without knowing the nature of the material being used. Thus, all states were invited to participate on the basis of administering vaccine to volunteers in the 2nd grade of school. Later the poliomyelitis incidence in these children would be compared with that in the uninoculated 1st and 3rd grade population. This study plan had certain scientific limitations, related primarily to possible bias, at all levels, in the follow-up of study children. Ob-

*In this Synopsis of the Summary Report of the Evaluation of 1954 Field Trial of Poliomyelitis Vaccine (Vaccine Evaluation Center, University of Michigan, Ann Arbor, Michigan, April 12, 1955) the original numbers are given for tables and for pages mentioned, in order to facilitate reference to the full report.

viously it was essential that nonvaccinated children be studied with the same degree of care as the vaccinated so that the discovery and diagnosis of cases of poliomyelitis in test and control groups would be strictly comparable. In order to achieve such an impartial comparison it was essential to introduce a so-called placebo control study into the existing plan. This type of study was carried out in 84 areas of 11 states signifying the interest in doing so (Table 1a). In 127 areas of 33 states the original, or observed control, study was carried out (Table 1b). The specific study areas were selected because of their consistently high poliomyelitis incidence during the past 5 years.

The tremendous clinic program was accomplished according to plan during April, May and June. In placebo control areas (Table 1a) the study population (1st, 2nd and 3rd grade) included 749,236 children; 455,474 (or 60.8%) requested participation; 200,745 (26.8%) received three injections of vaccine, and 201,229 (26.9%) three injections of placebo, an identical material which, however, contained no poliomyelitis virus or monkey kidney protein. In observed control areas (Table 1b) the study population totalled 1,080,680 children in the first

TABLE 1a.—DISTRIBUTION OF STUDY POPULATION BY PARTICIPATION STATUS AND VACCINATION STATUS—PLACEBO AREAS

Study Population	*Number*	*Percent*
Total Grades 1, 2 and 3	749,236	100.0
Total requests to participate	455,474	60.8
Complete series of injections:		
Vaccine	200,745	26.8
Placebo	201,229	26.9
Incomplete injections:		
Vaccine	8,484	1.1
Placebo	8,577	1.1
Absent at first clinic or withdrew	36,439	4.9
Number not requesting participation	280,868	37.5
Participation status not recorded	12,894	1.7

TABLE 1b.—DISTRIBUTION OF STUDY POPULATION BY PARTICIPATION STATUS AND VACCINATION STATUS—OBSERVED AREAS

Study Population	*Number*	*Percent of Second Grade*	*Percent of Total Population*
All Grades —Total	1,080,680		100.0
Requests	567,210		52.5
Second Grade—Requests	245,895	69.2	22.8
Complete vaccinations	221,998	62.4	20.5
Incomplete vaccinations	9.904	2.8	0.9
Absent or withdrew	13,993	3.9	1.3
First and Third Grades—Requests	321,315		29.7
All Grades—Participation not requested	332,870		30.8
Participation not recorded	180,600		16.7

three grades; 221,998 second grade children (20.5% of the total) received three doses of vaccine.

The first problem of evaluation was that of collecting and verifying basic information on each of the 1,829,996 children in the study population. These data which included the name, address, age, sex, history of poliomyelitis or other crippling condition, participation status and dates of vaccination, if any, for each child, were transferred to punch cards, and tables describing the population were prepared which would serve as the denominators over which the discovered cases of poliomyelitis would be placed for the determination of poliomyelitis attack rates in vaccinated versus control and in other segments of the population. During December, 1954, an interview survey was conducted on 1,100 study families in ten states in order to gain more insight into the differences existing between participants and nonparticipants (p. 13). This demonstrated striking differences in income level, community activity, health conveniences, education level, and others, which in turn assisted the center in deciding what control population would be most useful, in the observed control areas.

The question of safety of the vaccine (pp. 18 to 21 and 41 to 42) was assessed through specific studies of the cause and extent of absenteeism from school following inoculation in Pittsburgh, Pennsylvania, and Schenectady, New York. The experience was identical in vaccinated and control subjects and no significant reactions were observed. From records obtained during the clinic program, the following distribution of minor reactions was observed: Placebo control areas: 931 reactions or 0.4% in vaccinated and 939 or 0.4% in those receiving placebo. Of the so-called "major" reactions, none of which could be clearly attributed to inoculation, 9 or 0.004% occurred in vaccinated and 13 or 0.006% in the placebo control. These findings, plus other data referred to in the text, fail to implicate the vaccine as a significant cause of untoward reactions.

Also bearing on the question of safety is the review of 129 cases occurring up to the first month after inoculation (p. 20). Here again, there is no evidence implicating vaccine as a source of infection. Furthermore, study of the location of the paralysis failed to demonstrate any localization of involvement to the left arm, where all injections were given.

For the purpose of measuring the antigenic potency of the various lots of vaccine used, blood samples were collected prior to vaccination, 2 weeks after the 3rd clinic and again 5 months later from 40,881 children (p. 3). Results from the study of sera from 9,000 of these are now available for analysis and served as the basis for classifying lots of vaccine into good, moderate, low moderate and poor categories (pp. 21 to 25). There was wide variation in the response to various lots, as used under field conditions. In general, the response to Type 1 poliomyelitis virus was inferior to that for Types II and III. Data from the study of the third bleeding are less complete but indicate some persistence of antibodies 4 to 5 months after completion of the series of vaccinations. Some decline in antibody titer was observed, particularly in those children vaccinated with so-called poor lots; however, the levels in vaccinated children persisted in being distinctly higher than in the associated control children.

The second problem in evaluation was concerned with the discovery and investigation of all cases of poliomyelitis or suspected poliomyelitis in the study population. The various steps in the investigation are discussed at length

in the report, but consisted essentially in the initial case report; a clinical epidemiological report; muscle evaluation by one of 67 specially trained physical therapists 10 to 20 days and 50 to 70 days after onset of illness; the review of these findings by clinical experts; and the laboratory study of stool and blood samples from the patient, for the isolation of poliomyelitis or other virus and the search for poliomyelitis antibodies. An important phase to all the above studies and applying particularly to the work of the physical therapist and laboratories was the attempt to standardize the procedures used in all areas, so that the findings would be directly comparable in all segments of the study. Finally, rigid criteria were established for reaching the final diagnosis. Each study case was finally classified before the vaccination status was revealed, thus assuring unbiased interpretation of all data.

TABLE 2b.—SUMMARY OF STUDY CASES BY DIAGNOSTIC CLASS AND VACCINATION STATUS (RATE PER 100,000)

Study Group	Study Population	All Reported Cases		Poliomyelitis Cases						Not Polio***	
				Total		Paralytic		Non-paralytic			
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
All areas—total	1,829,916	1013	55	863	47	685	37	178	10	150	8
Placebo areas—total	749,236	428	57	358	48	270	36	88	12	70	9
Vaccinated	200,745	82	41	57	28	33	16	24	12	25	12
Placebo	201,229	162	81	142	71	115	57	27	13	20	10
Not inoculated*	338,778	182	54	157	46	121	36	36	11	25	7
Incomplete vaccinations	8,484	2	24	2	24	1	12	1	12	..	..
Observed areas—total	1,080,680	585	54	505	47	415	38	90	8	80	7
Vaccinated	221,998	76	34	56	25	38	17	18	8	20	9
Controls**	725,173	439	61	391	54	330	46	61	8	48	6
2nd grade not inoculated	123,605	66	53	54	44	43	35	11	9	12	10
Incomplete vaccinations	9,904	4	40	4	40	4	40	..	..	..	..

* Includes 8,577 children who received one or two injections of placebo.
** First and third grade total population.
*** Includes 73 cases of "doubtful polio."

Results. The comparison of the poliomyelitis attack rate in vaccinated and control populations is presented through a sequence of steps, each one attempting to purify further the diagnosis. A total of 1,013 cases was reported in the study population with onset during the period two weeks after the third vaccination clinic to December 31, 1954. These are classified in placebo control areas as follows: 67.5% paralytic, 17.6% nonparalytic, 7.2% doubtful, 7.6% not poliomyelitis.

As a first step, the total reported cases, total cases considered to be poliomyelitis, total nonparalytic and total paralytic in both placebo and observed control areas were examined (Table 2b). Through these stages of purification there is a progressive increase in the percentage of effectiveness displayed. No significant difference was detected in the rates of nonparalytic poliomyelitis in test and control groups. However, when these cases and those called not poliomyelitis are removed, so that only paralytic cases remain, an estimate of 75% of effectiveness is obtained in the placebo areas, and 62% in the observed areas.

Next (Tables 3a and 3b) more detailed attention was given to the effect of vaccine with respect to clinical type and extent of paralysis. The most strik-

TABLE 3a.—TOTAL REPORTED POLIOMYELITIS CASES IN STUDY POPULATION DISTRIBUTED BY VEC DIAGNOSIS, DEGREE OF PARALYSIS AND VACCINATION STATUS —PLACEBO AREAS.

VEC† Diagnosis by Degree of Paralysis	Number of Cases: Total No.	Total %	Vaccinated	Placebo	Not Inoculated	Rate per 100,000: Vaccinated	Placebo	S.L.	Not Inoculated
Total cases*	426	100.0	82	162	182	41	81	.001	55
Paralytic total	269	63.1	33	115	121	16	57	.001	37
Spinal	183	43.0	28	70	85	14	35	.001	26
Score 0	60		9	25	26	4	12	.01	8
1–19	44		9	12	23	4	6	N.S.	7
20–89	47		6	20	21	3	10	.01	6
90–199	23		2	9	12	1	4	.05	4
200+	9		2	4	3	1	2	N.S.	1
Unknown	..		..	..	..	..	..	..	..
Bulbar	14	3.3	3	5	6	1	2	N.S.	2
Bulbo-spinal	68	16.0	2	36	30	1	18	.001	9
Score 0	18		1	10	7	*	5	.01	2
1–19	20		..	13	7	..	6	.001	2
20–89	11		1	5	5	*	2	N.S.	2
90–199	14		..	6	8	..	3	.05	2
200+	5		..	2	3	..	1	N.S.	1
Unknown	..		..	..	..	..	..	..	..
Fatal polio	4	0.9	..	4	..	..	2	N.S.	..
Non-paralytic	87	20.4	24	27	36	12	13	N.S.	11
Doubtful polio	29	6.8	13	8	8	6	4	N.S.	2
Not polio	41	9.6	12	12	17	6	6	N.S.	5

* Excludes two cases who received partial injections.
S.L.—Level of statistical significance.
† VEC = Vaccine Evaluation Centers.

TABLE 3b.—TOTAL REPORTED POLIOMYELITIS CASES IN STUDY POPULATION DISTRIBUTED BY VEC DIAGNOSIS, DEGREE OF PARALYSIS AND VACCINATION STATUS —OBSERVED AREAS.

VEC Diagnosis by Degree of Paralysis	Number of Cases: Total No.	Total %	Vaccinated	Control Population	2nd Grade Not Inoc.	Rate per 100,000: Vaccinated	Control Population	S.L.	2nd Grade Not Inoc.
Total cases*	581	100.0	76	439	66	34	61	.001	53
Paralytic—total	411	70.7	38	330	43	17	46	.001	35
Spinal	247	42.5	20	199	28	9	27	.001	23
Score 0	79		12	63	4	5	9	N.S.	3
1–19	64		5	51	8	2	7	.01	6
20–89	67		2	53	12	1	7	.001	10
90–199	26		1	22	3	*	3	.05	2
200+	10		..	9	1	..	1	N.S.	1
Unknown	1		..	1	..	..	*	N.S.	..
Bulbar	25	4.3	3	20	2	1	3	N.S.	2
Bulbo-spinal	128	22.0	15	100	13	7	14	.01	11
Score 0	21		5	14	2	2	2	N.S.	2
1–19	38		6	29	3	3	4	N.S.	2
20–89	33		4	26	3	2	4	N.S.	2
90–199	11		..	9	2	..	1	N.S.	2
200+	23		..	20	3	..	3	.01	2
Unknown	2		..	2	..	..	**	N.S.	..
Fatal polio	11	1.9	..	11	..	..	2	N.S.	..
Non-paralytic	90	15.5	18	61	11	8	8	N.S.	9
Doubtful polio	44	7.6	12	26	6	5	4	N.S.	5
Not polio	36	6.2	8	22	6	4	3	N.S.	5

* Excludes 4 cases who received partial injections.
** Less than 1 per 100,000.
S.L.—Level of statistical significance.

ing effect was observed in bulbospinal disease, perhaps because this characteristic clinical pattern is so readily differentiated as being truly poliomyelitis. In this group, the estimate of effectiveness in placebo control areas was 94% with a lower limit of 81%. The effect noted in spinal paralytic polio was less striking, 60% with a lower limit of 39%. In observed control areas, these differences were even less pronounced but still highly significant.

A further refinement in analysis was to consider the effect of vaccine in patients from whom poliomyelitis virus was isolated (Tables 5a and 5b). These furnish a higher degree of confidence in diagnosis. In cases classified as spinal paralytic, the effectiveness was the same in placebo and observed control areas, 82 and 83% respectively, and the corresponding lower limits of effect were 65 and 64, respectively. Enforcement of laboratory criteria for diagnosis apparently eliminated a substantial number of cases which were less influenced by vaccination, and, undoubtedly among them, were many illnesses which actually were not poliomyelitis. The effect in bulbospinal poliomyelitis,

TABLE 5a.—REPORTED POLIOMYELITIS CASES IN THE STUDY POPULATION—LABORATORY POSITIVE*—PLACEBO AREAS

		Number of Cases			*Rate per 100,000*			
VEC Diagnosis	*Total*	*Vaccinated*	*Placebo*	*Not Inoculated*	*Vaccinated*	*Placebo*	*S.L.*	*Not Inoculated*
Total	198	18	86	94	9	43	.001	28
Non-paralytic	32	6	11	15	3	5	N.S.	4
Paralytic—Spinal	106	8	45	53	4	22	.001	16
Zero score	21	..	9	12	..	4	.01	4
Scores 1+	85	8	36	41	4	18	.001	12
Paralytic—Bulbar	10	2	4	4	1	2	N.S.	1
Paralytic—Bulbo-spinal	47	2	23	22	1	11	.001	7
Polio fatalities	3	..	3	..	..	1	N.S.	..

* Includes 170 cases with poliomyelitis virus isolated
23 no virus but 4-fold or greater rise in antibody in paired sera
5 no virus from patient but poliomyelitis virus recovered from a family member
S.L.—Level of statistical significance.

TABLE 5b.—REPORTED POLIOMYELITIS CASES IN THE STUDY POPULATION—LABORATORY POSITIVE*—OBSERVED AREAS

		Number of Cases			*Rate per 100,000*			
VEC Diagnosis	*Total*	*Vaccinated*	*Control*	*Not Inoculated*	*Vaccinated*	*Control*	*S.L.*	*Not Inoculated*
Total	300	25	248	27	11	35	.001	22
Non-paralytic	41	8	31	2	4	4	N.S.	2
Paralytic—Spinal	150	7	127	16	3	18	.001	13
Zero score	36	3	32	1	1	4	.05	1
Scores 1+	114	4	95	15	2	13	.001	12
Paralytic—Bulbar	17	1	15	1	**	2	N.S.	1
Paralytic—Bulbo-spinal	88	9	71	8	4	10	.01	6
Polio fatalities	4	..	4	..	..	1	N.S.	..

* Includes 253 cases with poliomyelitis virus isolated
42 no virus but 4-fold or greater rise in antibody in paired sera
5 no virus from patient but poliomyelitis virus recovered from a family member
** Less than 1 per 100,000.
S.L.—Level of statistical significance.

with laboratory confirmation superimposed, was 91% in placebo control and 60% in observed control areas.

The next step (Tables 6a and 6b) was to examine the effect of vaccine with reference to the specific type of poliomyelitis virus isolated. In placebo control areas the effectiveness was 68% against Type I, 100% against Type II

perience. If the results from the observed study areas are employed, the vaccine could be considered to have been 60 to 80% effective against paralytic poliomyelitis, 60% against Type I poliomyelitis, and 70 to 80% effective against disease caused by Types II and III. There is, however, greater confidence in the results obtained from the

TABLE 6a.—POLIOMYELITIS CASES IN THE STUDY POPULATION BY VIRUS DETECTION, SEROLOGY, TYPE OF VIRUS, AND BY VACCINATION STATUS—PLACEBO AREAS

	Number of Cases			*Rate per 100,000*			
Virus Detection and Serology	*Vaccinated*	*Control Population*	*Not** Inoculated*	*Vaccinated*	*Control Population*	*S.L.*	*Not Inoculated*
Virus Isolation Positive—Total	15	70	85	7	35	.001	24
Serology—Positive and probable	7	43	56	3	21	.001	16
Indefinite	6	13	23	3	6	N.S.	7
None	2	14	6	1	7	.01	2
Virus Type I—Positive—Total	13	39	49	6	19	.001	14
Serology—Positive and probable	6	27	32	3	13	.001	9
Indefinite	6	8	13	3	4	N.S.	4
None	1	4	4	*	2	N.S.	1
Virus Type II—Positive—Total	..	6	9	..	3	.05	3
Serology—Positive and probable	..	4	7	..	2	N.S.	2
Indefinite	..	..	1	..	..	..	*
None	..	2	1	..	1	N.S.	*
Virus Type III—Positive—Total	2	25	27	1	12	.001	8
Serology—Positive and probable	1	12	17	*	6	.01	5
Indefinite	..	5	9	..	2	.05	3
None	1	8	1	*	4	.05	*
Virus Isolation Negative—Total	23	27	30	11	13	N.S.	9
Serology—Positive and probable	8	17	16	4	8	.05	5
Type I	2	9	7	1	4	.05	2
Type II	2	5	3	1	2	N.S.	1
Type III	4	4	6	2	2	N.S.	2
Indefinite	12	5	6	6	2	N.S.	2
None	3	5	8	1	2	N.S.	2

* Less than 1 per 100,000.
** Includes 2 cases with incomplete injections.
S.L.—Level of statistical significance.

(significant at .05 level), and 92% against Type III. This clearly agrees with the previous demonstrations that most lots of vaccine were less antigenic against Type I than against the other two types. In addition, the effectiveness of different lots of vaccine varied considerably as measured by the occurrence of poliomyelitis.

"From these data it is not possible to select a single value giving numerical expression in a complete sense to the effectiveness of vaccine as a total ex-

strictly controlled and almost identical test populations of the placebo study areas.

"On this basis it may be suggested that vaccination was 80 to 90% effective against paralytic poliomyelitis; that it was 60 to 70% effective against disease caused by Type I virus and 90% or more effective against that of Type II and Type III virus. The estimate would be more secure had [a] larger number of cases been available."

OTHER STUDIES. Several supplemental analyses are presented in the body of the report, which have bearing on evaluation and are mentioned briefly here.

1) The effectiveness of vaccine in preventing cases of poliomyelitis classified by extent of paralysis on the basis of the first muscle examination was compared with that, based on the second muscle examination, which in essence, measured the extent of residual paralysis (Tables 9a and 9b). This later group demonstrated a much more striking preventive effect, which becomes more distinct as the severity of the disease increases.

2) Study (pages 39 to 41 and Appendix table) of the poliomyelitis attack rate by individual years of age in test and control groups serves to confirm the other observations on effectiveness, although in placebo control areas the difference seen in 6-year-old children was not statistically significant. There appears to be a progressive increase in effect as age increases, based on the limited data and narrow age span included in this study.

3) The poliomyelitis experience in the study areas of Massachusetts and central New York State is subjected to detailed analysis (pp. 43 and 44) since the reported disease in these areas was extremely mild and doubt exists as to whether many of the illnesses are due to poliomyelitis. Of the 44 cases reported from Massachusetts, poliomyelitis virus was recovered from only three. Unidentified, or so-called "orphan" viruses were recovered from 31

TABLE 6b.—POLIOMYELITIS CASES IN THE STUDY POPULATION BY VIRUS DETECTION, SEROLOGY, TYPE OF VIRUS, AND BY VACCINATION STATUS—OBSERVED AREAS

	Number of Cases			*Rate per 100,000*			
Virus Detection and Serology	*Vaccinated*	*Control Population*	*2nd** Grade Not Inoc.*	*Vaccinated*	*Control Population*	*S.L.*	*2nd Grade Not Inoc.*
Virus Isolation Positive—Total	20	210	22	9	29	.001	16
Serology—Positive and probable	10	144	15	5	20	.001	11
Indefinite	8	41	6	4	6	N.S.	4
None	2	25	1	1	3	.05	1
Virus Type I—Positive—Total	14	114	7	6	16	.001	5
Serology—Positive and probable	6	74	6	3	10	.001	4
Indefinite	6	26	..	3	4	N.S.	..
None	2	14	1	1	2	N.S.	1
Virus Type II—Positive—Total	2	34	2	1	5	.05	1
Serology—Positive and probable	2	26	2	1	4	.05	1
Indefinite	..	4	..	..	1	N.S.	..
None	..	4	..	..	1	N.S.	..
Virus Type III—Positive—Total	4	62	13	2	9	.001	10
Serology—Positive and probable	2	44	7	1	6	.001	5
Indefinite	2	11	6	1	2	N.S.	4
None	..	7	..	..	1	N.S.	..
Virus Isolation Negative—Total	30	103	20	14	14	N.S.	15
Serology—Positive and probable	6	62	9	3	9	.01	7
Type I	3	23	3	1	3	N.S.	2
Type II	2	13	2	1	2	N.S.	1
Type III	1	26	4	*	4	.01	3
Indefinite	22	36	10	10	5	N.S.	7
None	2	5	1	1	1	N.S.	1

* Less than 1 per 100,000.
** Includes 4 cases with incomplete injections.
S.L.—Level of statistical significance.

TABLE 9a.—VACCINATION STATUS OF PARALYTIC SPINAL AND BULBO-SPINAL STUDY CASES CLASSIFIED BY EXTENT OF PARALYSIS AS MEASURED BY BOTH THE 10–20 DAY AND 50–70 DAY MUSCLE EXAMINATIONS—PLACEBO AREAS

Type and Extent of Muscular Involvement

Based on 10–20 Day Muscle Examination *Based on 50–70 Day Muscle Examination*

TABLE 9a.—VACCINATION STATUS OF PARALYTIC SPINAL AND BULBO-SPINAL STUDY CASES CLASSIFIED BY EXTENT OF PARALYSIS AS MEASURED BY BOTH THE 10–20 DAY AND 50–70 DAY MUSCLE EXAMINATIONS—PLACEBO AREAS

	Type and Extent of Muscular Involvement													
	Based on 10–20 Day Muscle Examination							*Based on 50–70 Day Muscle Examination*						
					Combined Spinal and Bulbo-spinal with Score							*Combined Spinal and Bulbo-spinal with Score*		
Vaccination Status	*Total*	*Total Excluding Spinal Zero Score*	*Spinal Zero Score*	*Bulbo-spinal Zero Score*	*1–19*	*20+*	*Unk.*	*Total*	*Total Excluding Spinal Zero Score*	*Spinal Zero Score*	*Bulbo-spinal Zero Score*	*1–19*	*20+*	*Unk.*
Total	251	193	58*	15	57	101	20	251	159	92	31	49	77	2
Vaccinated	30	22	8	1	8	11	2	30	12	18	1	5	6	..
Placebo	106	82	24	8	22	44	8	106	73	33	17	23	31	2
Not Inoculated	115	89	26	6	27	46	10	115	74	41	13	21	40	..
Ratio *Placebo* Cases Vaccine	3.5	3.7	3.0	8.0	2.7	4.0	4.0	3.5	6.1	1.8	17.0	4.6	5.2	..

* One additional case had spinal paralytic polio with zero score on both examinations but who received only two inoculations of vaccine.

TABLE 9b.—VACCINATION STATUS OF PARALYTIC SPINAL AND BULBO-SPINAL STUDY CASES CLASSIFIED BY EXTENT OF PARALYSIS AS MEASURED BY BOTH THE 10–20 DAY AND 50–70 DAY MUSCLE EXAMINATIONS—OBSERVED AREAS

	Type and Extent of Muscular Involvement													
	Based on 10–20 Day Muscle Examination							*Based on 50–70 Day Muscle Examination*						
					Combined Spinal and Bulbo-spinal with Score							*Combined Spinal and Bulbo-spinal with Score*		
Vaccination Status	*Total*	*Total Excluding Spinal Zero Score*	*Spinal Zero Score*	*Bulbo-spinal Zero Score*	*1–19*	*20+*	*Unk.*	*Total*	*Total Excluding Spinal Zero Score*	*Spinal Zero Score*	*Bulbo-spinal Zero Score*	*1–19*	*20+*	*Unk.*
Total*	375	301	74	19	83	165	34	375	247	128	59	74	111	3
Vaccinated	35	23	12	5	10	6	2	35	17	18	8	6	3	..
Control	299	240	59	13	64	137	26	299	200	99	43	64	90	3
2nd Grade Not Inoculated	41	38	3	1	9	22	6	41	30	11	8	4	18	..
Vaccinated x factor**	115	76	39	16	33	20	7	115	56	59	26	20	10	..
Ratio *Control* Cases Vaccine	2.6	3.2	1.5	0.8	1.9	6.9	3.7	2.6	3.6	1.7	1.7	3.2	9.0	3/0

* Four paralytic cases with zero score on second examination were incompletely vaccinated and are not shown in this table.

** Since control population in 1st and 3rd grades was 3.28 times as large as the population of completely vaccinated children, the number of cases in vaccinates is multiplied by this factor in order to put them on a comparable population base.

A somewhat similar experience occurred in central New York State. In these areas the effect of vaccine was much reduced or difficult to detect. The role of the "orphan" viruses in causing illness has not been established and needs further study.

4) The studies carried on in Canada and Finland (pp. 44 to 46) were limited in scope and differed somewhat in design. However, despite the small number of cases of poliomyelitis occurring in study children, a significant preventive effect was demonstrated on refined analysis.

5) A major activity in the Field Trial areas was the investigation of all cases of poliomyelitis, where a study child resided in the household. Analysis of these data (p. 47) in placebo control areas indicates that among the 233 vaccinated children exposed to a case of poliomyelitis in the family, only one developed a laboratory confirmed illness, a Type I infection (0.43%). On the other hand, among 244 children who had received placebo and were exposed under similar circumstances, 8 developed laboratory confirmed poliomyelitis (3.28%). This is a statistically significant difference. This was not correspondingly distinct in the observed study areas.

6) Although it was urged that gamma globulin not be used in the study population during the course of these investigations, inevitably some was used for measles and hepatitis prophylaxis and for both family contact and mass application in connection with poliomyelitis. Records of this use were collected and the tabulation indicates that during the period May 1 to December 31, in placebo control areas, only 0.9% of the vaccinated children and 1.1% of those given placebo received some gamma globulin.

In observed control areas the use was even less, 0.4% in both the test and control groups. No matter what one believes about the practical effectiveness of gamma globulin in preventing poliomyelitis, the total use of this material and its equal distribution in vaccinated and nonvaccinated children indicates that it did not interfere with proper evaluation of the effectiveness of vaccine.

7) Attention is called to Tables I and II of the Appendix which present the distribution of cases by diagnostic classification and vaccination status in each of the 211 study areas. This should provide information of interest for each local area. The limited scope of the summary report makes it impossible to present further details of analysis for each study area separately.

OBSERVATIONS ON THE REGIONAL CIRCULATION DURING PHARMACOLOGICALLY INDUCED HYPOTENSION

By E. F. Hueber, M.D.

(From the First Department of Medicine of the University of Vienna, Vienna, Austria, Prof. Dr. E. Lauda, Chief of Service)

The introduction of new potent blood pressure depressants such as hexamethonium, protoveratrine or the hydrazophthalazines into medical practice has opened a new field for the treatment of hypertension. Encouraging therapeutic results were reported from all over the world[13]. The mechanism of the action of these depressants was investigated by reliable hemodynamic studies[7-10,12]. Considerable changes in the regional blood flow in the various vascular beds and in the pressure constants of the circulation were observed during the phase of pharmacologically induced hypotension[1-4,14-17,19,22,23]. While each drug produced different changes in the regional circulation, these changes seemed to be specific for a given drug. In addition to the changes in regional circulation noted during the induced hypotension, integrative action on the whole organism, as, for example, a dangerous fall in blood sugar during an operation with controlled hypotension[11], was reported.

These findings have an important bearing in the selection of the new drug for the treatment of hypertensive vascular disease. We conducted, therefore, three types of studies to investigate the influence of these agents on renal circulation and in the whole organism: 1) A study of renal function. 2) An investigation of possible changes in extracellular fluid and some other constituents of the blood during the period of induced hypotension. 3) The investigation of circulation time during this induced hypotensive phase.

Methods. 1) The kidney function was determined before and during the acute stage of induced hypotension by clearance methods. The inulin and PAH-clearance tests were used, and the filtration fraction as well as resistances in the vas afferens and efferens, the resistance in the renal veins and the total resistance expressed in mm. Hg/min./cc. times $7.992 = \text{Dyn. sec. cm.}^{-5}$ were determined.

The hypotensive drugs were given in a dosage which caused a drop in blood pressure of at least 20% without creating unpleasant or dangerous side reactions.

2) In order to record changes in permeability within the entire capillary bed during the phase of pharmacologic depression of the blood pressure in hypertensive individuals certain blood constituents were analyzed. In 10 patients the systemic arterial pressure, the hematocrit, the density of the serum of whole blood and blood cells were determined before and during the induced depression of the blood pressure. The density was determined gravimetrically with Pregel's precision pipettes in collaboration with H. Scheid (see Method, Scheid[20]).

Results. In the upper columns of the Figs. 1 to 5, one can see that the various depressants PVS (Puroverine, Sandoz), Regitine, the hydrazophthalazines Apresoline and Nepresol, and Depressin (hexamethonium) almost invariably depress kidney function during the phase of pharmacologic hypotension of the systemic blood pressure. It is apparent that only the onset, degree and duration of this action vary with the various depressants. The urine total volume decreases invariably simultaneously with the blood

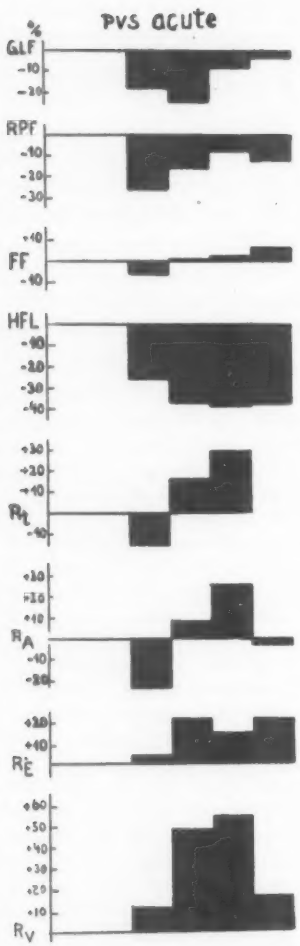

Fig. 1

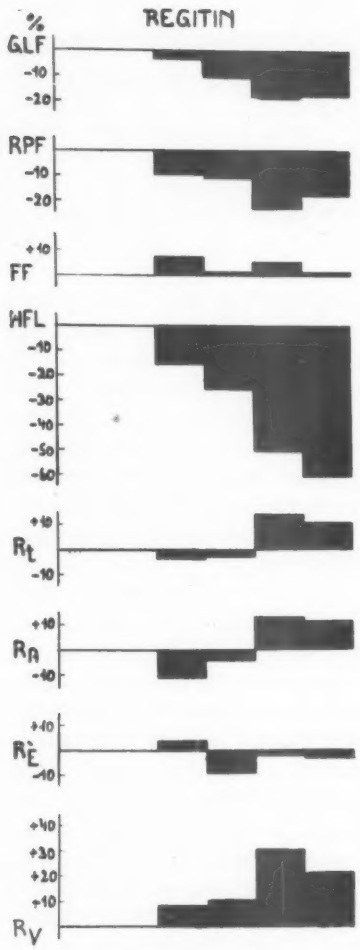

Fig. 2

Fig. 1.—Effects of a 20% fall in blood pressure, induced by Puroverine (PVS), on renal function, expressed in % change from prehypotensive values.

GLF = glomerular filtration rate cc./min.
RPF = renal plasma flow cc./min.
FF = filtration fraction.
HFL = urine flow cc./min.
R_t = total vascular resistance.
R_A = resistance in afferent vessel.
R_E = resistance in efferent vessel.
R_V = resistance in renal vein.

Fig. 2.—Effects of Regitin on renal function in hypertensive patients. (See Fig. 1 for key to abbreviations.)

pressure fall. This shutdown of urine production may be interpreted as a balance for the energy loss through decreased kidney function. Using the Lamport method for the determination of vascular resistance, we found the resistance in the vas afferens and efferens, in the renal vein and consequently the total resistance to be changed in a different way depending on the various drugs used. Apresoline, for example, was found to increase the total resistance, while hexamethonium mainly depressed it. With Protovera-

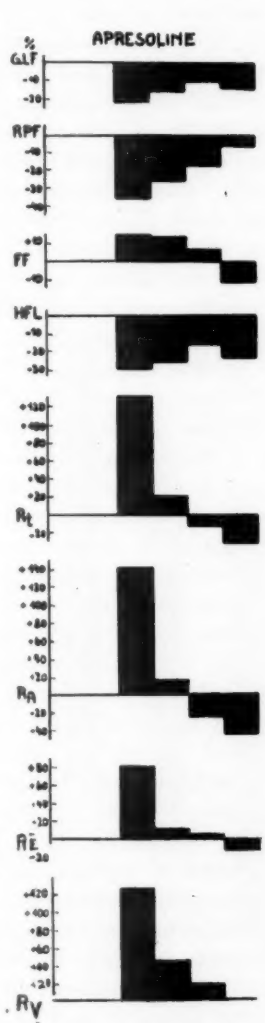

Fig. 3

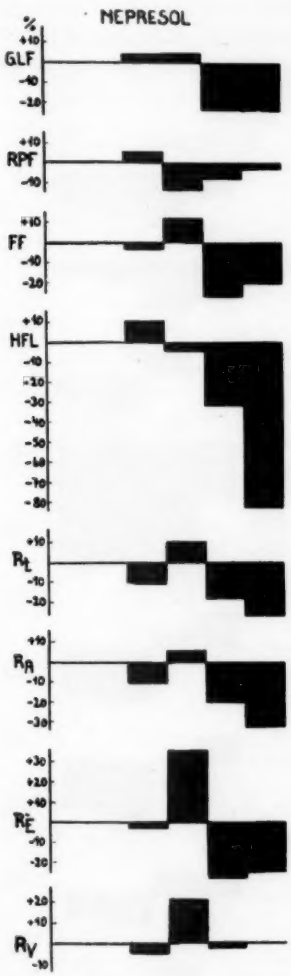

Fig. 4

Fig. 3.—Effects of Apresoline on renal function in hypertensive patients. (Note increase of total resistance.) (See Fig. 1 for key to abbreviations.)

Fig. 4.—Effects of Nepresol on renal function in hypertensive patients. (See Fig. 1 for key to abbreviations.)

trine the total resistance was lowered in the first phase of hypotension and later slightly increased.

In Figs. 6, 7 and 8, the columns represent average values obtained in 10 experiments and are expressed in percentage deviation from the mean values taken under basal metabolic conditions. The mean systemic pressure (see Fig. 6) drops sharply 15 minutes after the intravenous injection of 0.2 mg. Purotrine. This drop becomes highly significant 25 minutes after injection. One can see that the hematocrit falls simultaneously. This fall is statistically significant and remains so during the rest of the test. The phenomenon would indicate that the blood has become more liquid with the drop in blood pressure and is interpreted in Figs. 6 and 7. It is obvious that this thinning of the blood is caused by an increase in the fluid of the serum and consequently in the whole blood. The fluid content of the blood cells and, accordingly, their density remain unchanged (see Figs. 7 and 8). It can be seen that the mean values for the density of the serum and whole blood drop simultaneously with the decrease in blood pressure (see Fig. 8). According to Schade's theory of equilibrium of hydration, one would assume that the decrease in osmotic pressure following a reduction of blood pressure is caused by the dehydration of the connective tissue cells, while the cells of the vascular walls become hydrated. Such a process may be in part responsible for maintenance of the normal equilibrium of the cardiovascular system in the course of a successful reduction in blood pressure in hypertensives. This has also been reported by Scheid and Siedek[21] in the treatment of this condition with iodine.

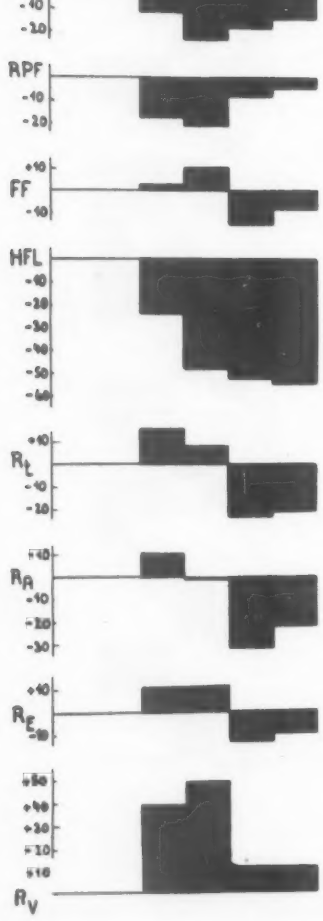

Fig. 5.—Effects of Depressin (hexamethonium) on renal function in hypertensive patients. (See Fig. 1 for key to abbreviations.)

In studies of 20 hypertensive patients the circulation time (Decholin time) remained within normal limits when these patients were studied in the lying position and had a moderate 20 to 30% decrease in their blood pressure. This was true provided that these patients were found to have a circulation time within normal limits during the control period. No side effects were elicited or volunteered by the patients during this period of induced hypotension. Even when greater decreases in blood pressure were induced, the circu-

lation time remained normal until further decreases were induced or when circulatory collapse or shock was noted or when the patient assumed the standing position. At this time the values for circulation time rose significantly above normal. Obviously the homeostatic regulation maintains the blood flow to the organs by continuous readjustments as long as possible. The homeostatic principle is thrown out of balance only with a breakdown of this equilibrium and this causes the circulation time to rise. It is well known that even at that time a new equilibrium is re-established which maintains the blood flow to the vital organs. This new equilibrium has been called that of "centralized circulation" (Duesberg and Schroeder[6]). At this point the circulation time becomes shorter again and reveals a false normal value.

Discussion. Our studies as well as those of others[1-4,14-17,19,22,23] revealed that as a consequence of the use of the hypotensive drugs in the treatment of hypertension certain parts of the vascular system show an increasing

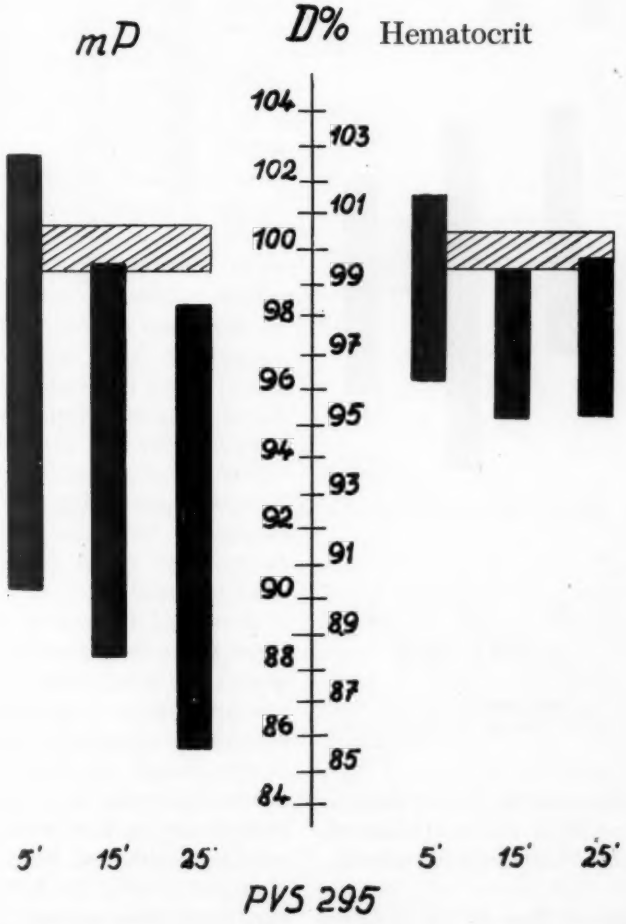

Fig. 6.—Effect of Puroverine (average of 10 determinations) on mean systemic pressure (mP), density (D%) and hematocrit.

depth of ischemia or reduced blood flow. This was apparent for all drugs in our studies on the kidney blood flow. However, in the use of moderate dosages of these drugs we found, in further clinical studies with long-term therapy in hypertensives, that the tendency of decrease in blood flow to a given area could be counterbalanced, presumably by homeostatic mechanisms.

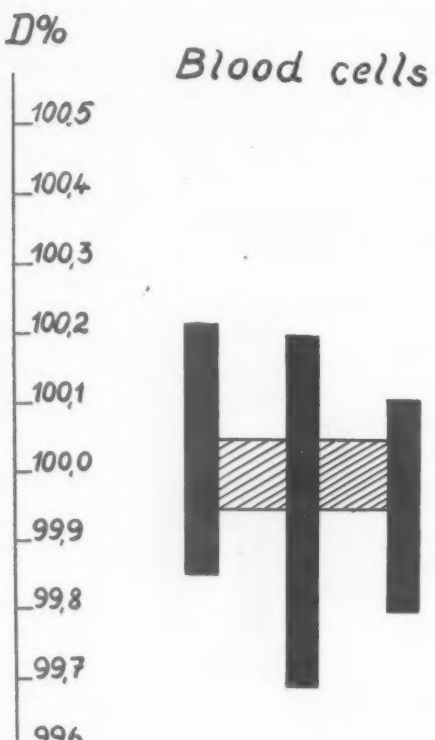

Fig. 7.—Effects of Puroverine (average of 10 determinations) on the density of erythrocytes.

When the blood flow to the kidneys decreases, we noted a simultaneous decline in urine output, indicating that the work of this particular organ has been decreased. One would expect, in view of the decrease in renal blood flow caused by the use of hypotensive agents treated over a long term in this way, that the patients would show evidence of increasing renal failure. Six hypertensive patients with laboratory evidence of beginning renal decompensation were treated over a long period with Puroverine. The blood pressure was fairly well controlled to constant low levels. During this period we did not find any clinical or laboratory evidence of increasing renal insufficiency.

We cannot say from this study whether our failure to observe increasing renal decompensation meant that this drug when used intermittently over a 24-hour period was not sufficiently active to cause such an undesirable effect. It may be, however, that due to the vascular re-adjustments in the kidney, operating through homeostatic mechanisms, the renal failure, which might be theoretically expected on the basis of our acute studies, fails to appear in a long-term treatment. Reubi[18] and Deutsch[5] have shown with blood pressure depression under Hydergine that the renal circulation decreases during the acute hypotensive period while under effective long-term treatment with the same drug no reduction of renal function could be demonstrated.

It was of interest to us to find that during the hypotensive phase, resulting from administration of Puroverine and other hypotensive drugs, the hematocrit decreased, while the density of the blood corpuscles remained the same, indicating that hemodilution occurred during this period.

The circulation time remained unchanged during the fall in blood pressure from administration of the various hypotensive drugs until vascular collapse became imminent. At this point

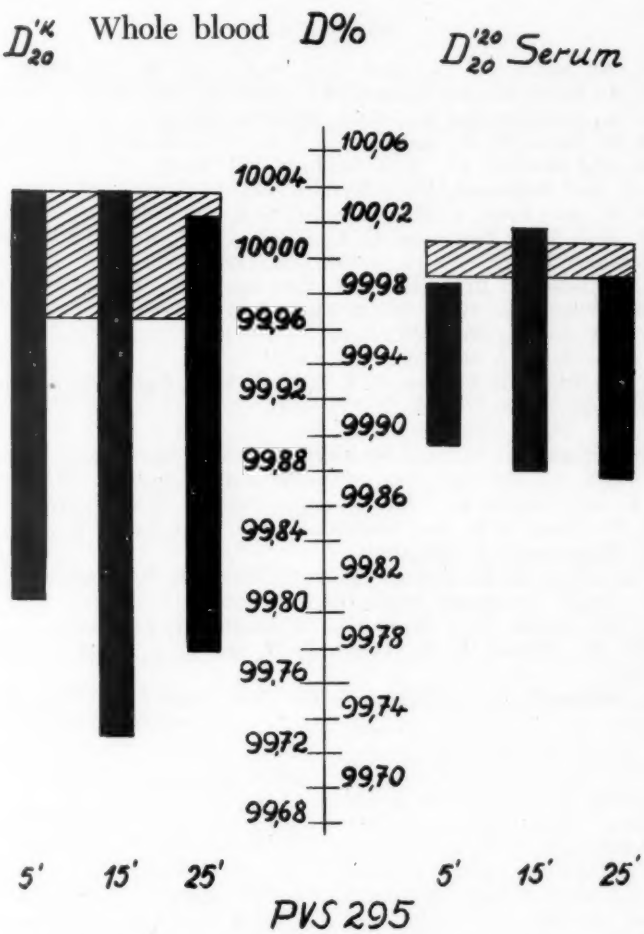

Fig. 8.—Effect of Puroverine (average of 10 determinations) on the density of whole blood and serum.

the circulation time became rapidly prolonged. In other words, a homeostatic mechanism comes into operation to maintain a steady internal state until the limits of elasticity of this mechanism were reached. In a later stage of reduced "centralized circulation" a normal circulation time may again be found. At this point the circulation time expresses a false value on the efficiency of circulation.

Summary. 1) During effective blood pressure reduction in hypertensive patients with moderate renal decompensation, no increase in renal failure was observed under treatment with Puroverine, a new powerful hypotensive drug. Marked changes, however, take place in renal circulation during the acute hypotensive phase with all strong depressants.

2) During the acute period of blood-pressure depression, hemodilution occurs.

3) In therapeutically induced hypotension the circulation time remains normal. With further blood-pressure depression, vascular collapse is evoked. At this point the circulation time becomes rapidly prolonged.

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THE CLINICAL USE OF CORTICOTROPIN (ACTH) AND ADRENAL CORTICOSTEROIDS IN THE THERAPY OF INTRACTABLE EDEMA*

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The present day therapy of edema possesses certain inadequacies. Although the treatment of edema has to a great extent been satisfactory, a state of "refractoriness" to treatment eventually occurs. The use of corticotropin (ACTH) and corticosteroids in patients with refractory edema of both nephrotic and cardiac origin has dramatically reversed this state.

The observation that adrenal corticosteroids and the antidiuretic hormone (ADH) play important roles in edema formation has been satisfactorily established. Animal experimentation has shown that adrenal corticosteroids exert a significant effect in the regulation of water balance as well as electrolyte balance. The electrolyte effect of these steroids has been stressed in clinical practice; but, their effects on water metabolism have not received adequate attention. The use of these hormones in the past has proven to be of therapeutic benefit in patients with the nephrotic syndrome. The basic pathophysiology of cardiac edema differs little from that present in the nephrotic syndrome. Therefore, the clinical use of ACTH in "refractory" or "terminal" cardiac edema was begun by one of us (FRS) 3 years ago. It is the purpose of this report to present a résumé of our experiences gathered during their use in "refractory" edema states.

Methods and Materials. Ten patients with the nephrotic syndrome, 21 patients with "refractory" cardiac edema, and 2 cardiac patients with the sodium-dilution syndrome are included in this study. The diagnosis of the nephrotic syndrome was based on conventional criteria. The 21 patients with cardiac disease included 8 with arteriosclerotic cardiovascular disease, 8 with rheumatic heart disease, 3 with hypertensive heart disease, and 2 with chronic cor pulmonale. All studies were performed on a Metabolic Unit with its own laboratory and diet kitchen. The interested reader is referred to a previous publication for details as to the Unit's organization and the extensive metabolic studies routinely performed on patients with edema[35].

Daily balance studies for sodium were done. Urinary and plasma sodium concentrations were determined by a method using the Beckman flame photometer. The daily intake of sodium for the food actually ingested was calculated from the data given by Bowes and Church[7]. Fecal and skin losses of sodium were estimated according to the report of Arn and Reimer[2]. Daily fasting weights were recorded on a scale sensitive to 100 gm.

Results. Graphic representations and case histories of illustrative cases only are presented in order to conserve space.

Patients with edema that is refractory to the usual therapeutic measures

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have shown three different modes of response to hormonal therapy.

1. The usual mode of diuresis induced by the administration of ACTH to patients with the nephrotic syndrome is an abrupt, spontaneous diuresis in the days following the discontinuance of ACTH therapy[3,14,19,26,27].

Diuresis of this type usually begins in the first 24 hours after ACTH has been stopped[19]. This pattern has similarly been observed by us in patients with edema of cardiac origin[10]. The diuresis is most often water in excess to sodium in both types of patients; although, proportionate losses of water and sodium and sodium loss in excess to water also occur[19]. This mode of diuresis induction is illustrated by Fig. 1.

2. Edema loss may also occur *during* the administration of ACTH[3,19,26,27]. This mode of diuresis was again noted in both renal and cardiac patients[10]. Diuresis and negative sodium balance

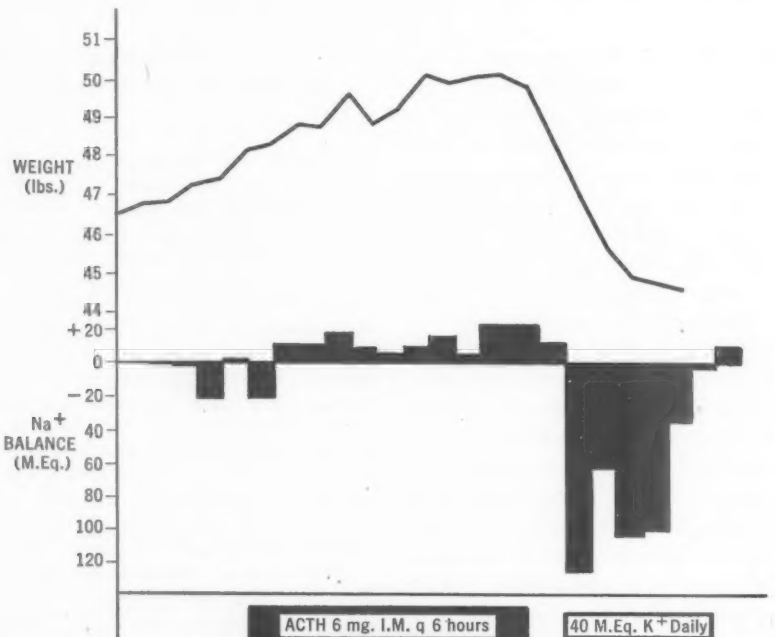

Fig. 1.—The graphic representation of a 5-year-old male with the nephrotic syndrome who developed edema in the summer of 1951. His course was variable in intensity but was progressively more severe. He was first treated by us in December, 1953. At that time he was markedly edematous, had ascites and a severe anemia. He was hospitalized for a period of 98 days and his course was variable, being associated with repeated upper respiratory infections. A 7-day course of ACTH in February, 1954, produced edema loss and subjective improvement. He was readmitted in July, 1954, after he again developed a slowly progressive edema and ascites which followed the onset of a moderately severe diarrhea. He again received ACTH. This course of therapy is the one illustrated. It is of additional interest to note that diarrhea stopped after 3 doses of ACTH.

This graph illustrates weight gain and sodium retention during the course of ACTH and abrupt, spontaneous weight loss and negative sodium balance after the hormone was discontinued. A similar pattern was observed in 5 additional patients with the nephrotic syndrome[19], and in 4 patients with edema of cardiac origin[10].

usually begin about the fifth or sixth day of hormone therapy. Again, all variations of water and sodium balance may be encountered. Proportionate amounts of water and sodium as well as disproportionate amounts of one or the other may be lost[19]. Figures 2 and 3 illustrate the type of patient in whom diuresis begins during ACTH therapy.

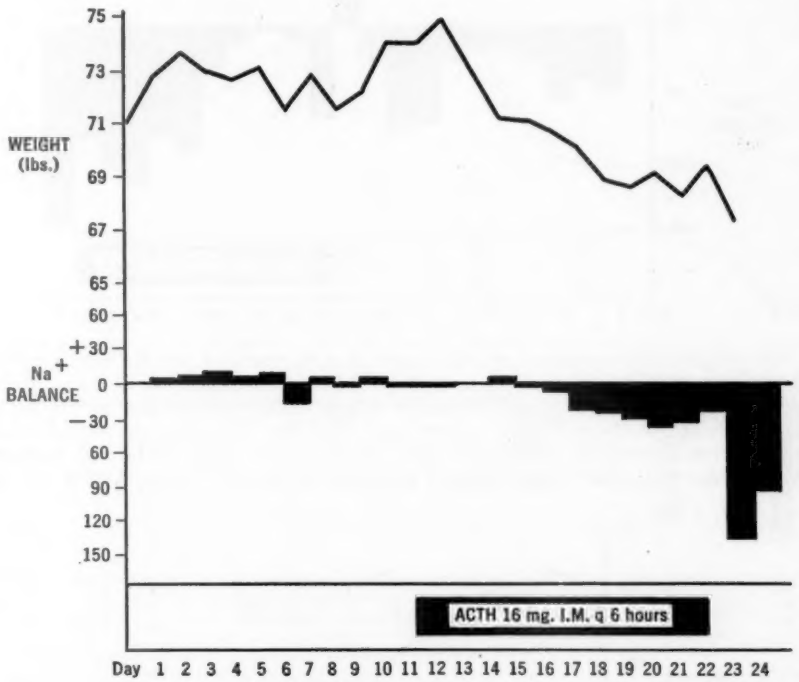

Fig. 2.—The course of an 11-year-old nephrotic female whose edema was first noted in January, 1953. Her clinical course was rapidly progressive. She received ACTH as represented graphically in April, 1953. Sodium diuresis and edema loss began during the administration of ACTH as well as after its discontinuance. Water was lost in excess to sodium during ACTH therapy in this patient while sodium was lost in disproportionate amounts following its discontinuance. Two additional patients with nephrosis began a spontaneous diuresis during hormone therapy[19].

3. ACTH by some as yet unknown mechanism can cause renal tubules to regain their "sensitivity" to mercurial diuretics in patients who had become refractory to their administration[19]. This is illustrated in Figs. 4 and 5. ACTH may also change the qualitative response of the kidneys to mercurial diuretics as well as the quantitative change described above. This phenomenon is illustrated in Fig. 6.

Edema loss by any of the three methods described above was obtained in 8 of the 10 patients with the nephrotic syndrome[19]; and in 18 of 21 patients with edema of cardiac origin[10].

The use of adrenal corticosteroids in 2 cardiac patients with the sodium dilution syndrome demonstrates the induction of a selective water diuresis without an associated sodium diuresis. Plasma sodium values returned to normal during corticosteroid administra-

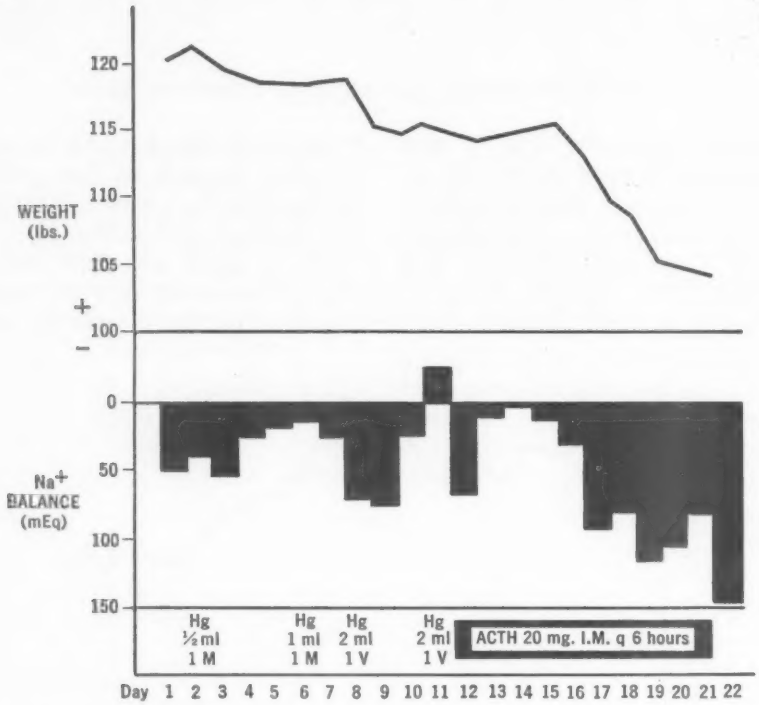

Fig. 3.—The graphic representation of the course of a 61-year-old female who was in severe cardiac decompensation due to hypertensive-arteriosclerotic cardiovascular disease. Edema had become resistant to all forms of management. It will be noted that sodium and water diuresis began spontaneously on the sixth day of therapy. She lost all edema during and following ACTH administration without the use of mercurial diuretics. Four additional patients with refractory edema of cardiac origin began a spontaneous diuresis during ACTH therapy[10].

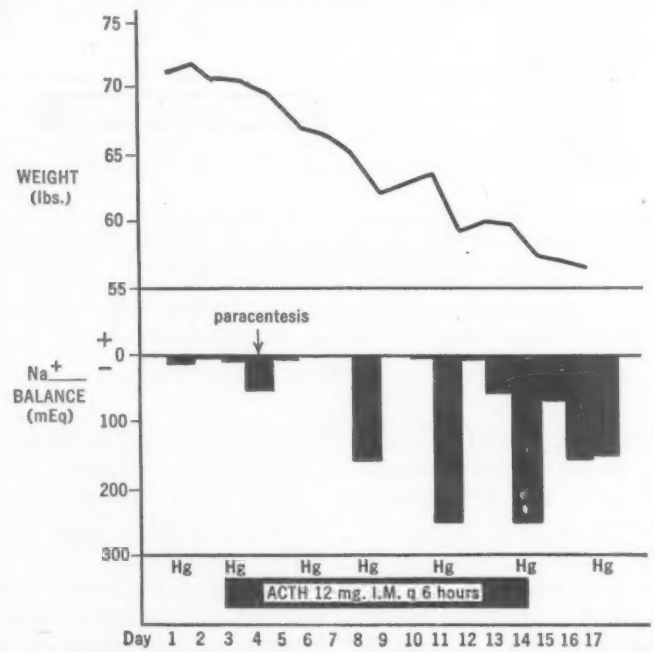

Fig. 4.—The data of a 7-year-old male with nephrosis who was first treated on the Metabolic Unit in the summer of 1948. He was maintained relatively edema-free and subjectively well until November, 1951. An upper respiratory infection initiated marked, generalized edema at that time. All of the usual measures failed to relieve his edema. He did not respond to mercurial diuretics. A course of ACTH and mercurial diuretics was instituted. It can be noted from this figure that the renal tubular reaction to mercurials improved greatly during and after hormone therapy. Two additional patients with nephrosis regained their "sensitivity" to mercurial diuretics[19].

tion. The mechanisms of this phenomenon are discussed in detail in the discussion to follow. Results obtained by the more specific use of adrenal corticosteroids in these 2 patients allow us to explain many of the beneficial effects of ACTH in the therapy of resistant edema. These 2 patients are represented graphically in Figs. 7 and 8.

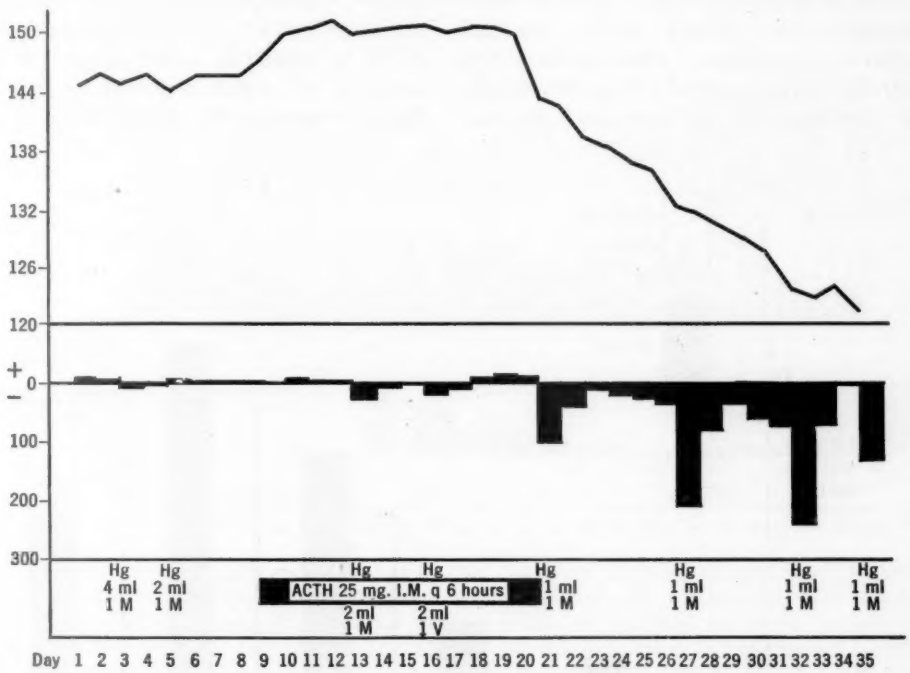

Fig. 5.—The graphic representation of a 63-year-old male with severe arteriosclerotic cardiovascular disease. His edema was refractory to the usual measures. Note the lack of response to mercurial diuretics before ACTH administration and the increasing responsiveness of the kidney to mercurials during and after hormone therapy. Five additional patients with cardiac edema regained their "sensitivity" to mercurial diuretics[10].

Discussion. Intractable, "terminal," cardiac edema has responded dramatically to the use of ACTH and adrenal corticosteroids in many of our patients. The use of these hormones in the presence of edema, especially that of cardiac decompensation, has been contraindicated because of the known sodium-retaining capabilities of these compounds. However, the profound influence of these compounds on the regulation of water balance has been generally overlooked. The following discussion is a résumé of previous animal and clinical experiments on which the rationale of the use of these compounds in patients with edema is based.

The important role of the kidneys in the sodium retention and edema formation of cardiac decompensation has been established only recently[39,43]. The role of the kidneys has been further elaborated by numerous authors[8,9,20,21,30,31]. At first the mechanism of increased sodium reabsorption

by the renal tubules in heart failure was felt to be due to alterations in renal hemodynamics[40]. More recently hormones from the adrenal cortex have also been implicated in this mechanism. An excessive outpouring of adrenal corticosteroids in the urine during cardiac decompensation was observed[4,28,32]. It is believed that these hormones cause an excessive renal tubular reabsorption of sodium with resultant edema formation. Abnormally high adrenal corticosteroid production might be explained by an increased production of ACTH as has been reported in a series of patients with acute cardiac decompensation[6].

The role of the antidiuretic hormone (ADH) in the formation of edema has also become of increasing importance[33,42]. Increased amounts of ADH have been detected in the sera and urine of patients with edema due to cardiac decompensation, nephrosis, and hepatic disease[4,13,33,44]. The function of ADH is primarily a regulation of the amounts of water reabsorbed by the distal tubular cells of the kidney. In-

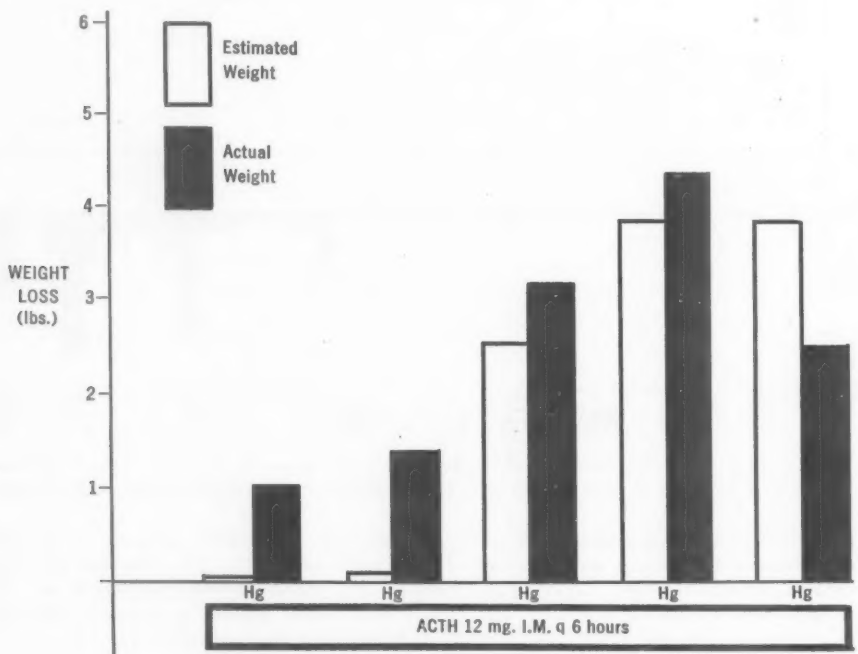

Fig. 6.—Another graphic representation of the patient shown in Fig. 4. Five injections of mercurial diuretic (0.5 cc. subcutaneously) were given during ACTH therapy. The patient had shown little response to mercurials before his admission to the Unit. Estimated weight loss as illustrated was based on negative sodium balance data obtained daily. It has been our experience that estimation of extracellular fluid loss by sodium balance studies has given a closer approximation of actual weight loss than either thiocyanate or D_2O space determinations[35]. Therefore, if actual weight loss exceeds estimated weight loss it would mean a diuresis of water in excess to sodium. It can be noted from this graph that early in the course of ACTH water was lost in excess of sodium when mercurial diuretics were given. Later in the course of hormone therapy sodium is lost in excess of water following mercurial administration.

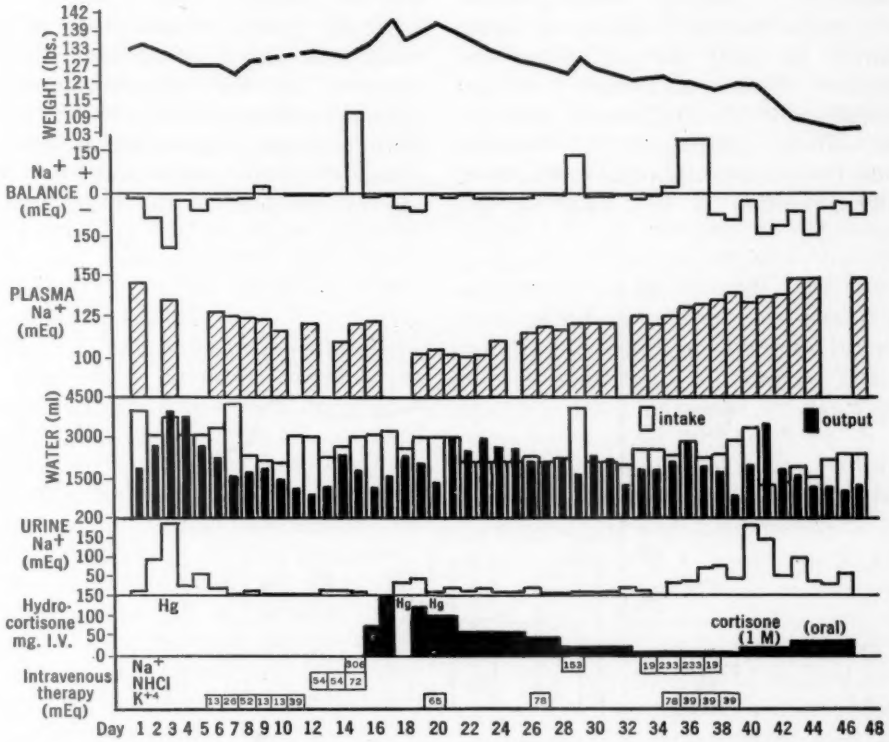

Fig. 7.—The data obtained from the study of a 63-year-old female with hypertensive, arteriosclerotic, cardiovascular disease and mild, chronic uremia. She had had several episodes of cardiac decompensation prior to this admission and had not been completely edema free for several months. A short time before this admission she developed a left-sided hemiplegia. The patient was admitted in moderate congestive failure. She was mentally alert although a complete, flaccid, left-sided hemiplegia was present. At first the patient responded well to the usual anti-edema regimen. However, as can be noted from this figure her weight began to increase. A marked fall in plasma sodium concentration occurred. Her urine output dropped and she entered into a sodium-dilution syndrome with deep, unresponsive coma. The plasma sodium dropped to 105 mEq./L. The infusions of saline failed to correct the low sodium but only increased her edema. Mercurial diuretics caused further sodium loss without water loss. Potassium and ammonium chloride infusions failed to initiate a diuresis. Therefore, hydrocortisone therapy intravenously was begun.

It can be noted from the accompanying graph that the adrenal corticosteroid initiated a selective water diuresis. Sodium was retained despite large urine volume. The plasma sodium concentration gradually returned to normal and the state of coma cleared. As plasma sodium values approximated normal it can be seen that "salt-loading" both intravenously and later orally resulted in a normal urinary excretion of the excess sodium given while cortisone was being administered. It must be emphasized that this occurred in a kidney that had previously been unable to manage even extremely low amounts of sodium without edema formation. The patient has been maintained free of edema on a dosage schedule of 12.5 mg. of cortisone orally b.i.d. without the adjunctive use of mercurial diuretics.

creased amounts of ADH cause increased water retention.

Strikingly, adrenal corticosteroids have shown profound effects on water balance as well as on electrolyte balance[18]. Water is excreted at abnormally low rates in humans who exhibit adrenal insufficiency[22,25,34,36,37,41]. It has been shown that the low rate of water excretion is the result of increased tubular reabsorption of water due to an abnormally high concentration of ADH[5]. This tendency for increased water reabsorption in patients with adrenal insufficiency can be reversed by the administration of adrenal corticosteroids[1,11,12,15,17,18]. That there is an antagonistic action between adrenal corticosteroids and the antidiuretic hormone in the regulation of

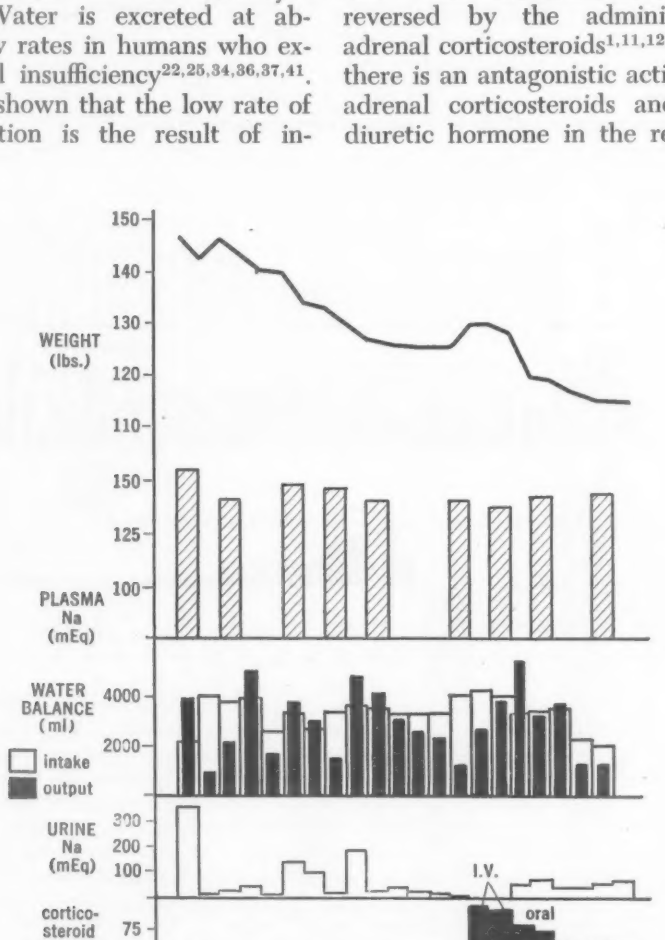

Fig. 8.—A 71-year-old male who had had slowly progressing, untreated, congestive failure for about one year before admission. He had arteriosclerotic, coronary artery disease as well as rheumatic mitral stenosis. It can be noted from this figure that the usual anti-edema regimen was initially satisfactory. However, on the 14th hospital day his weight suddenly increased 4 pounds; his urine output fell; and the concentration of plasma sodium decreased. It was felt that he was entering into a sodium dilution syndrome. Adrenal corticosteroid therapy was initiated at that time. Note the rather marked diuresis of water with selective retention of sodium and weight decrease. Here again, as the plasma concentration of sodium returned to normal the urinary excretion of unwanted sodium rose. This pattern continued and the patient became edema free without further mercurial therapy.

water balance appears evident. It is not certain whether adrenal corticosteroids physically or chemically oppose the effect of an increased concentration of ADH; or, whether the administered adrenal corticosteroids counteract the unopposed antidiuretic action of ADH in the renal tubules in patients with adrenal insufficiency. Both mechanisms may be active in the same patient. The possibility that a more complex mechanism than a simple "push-pull" mechanism forms the basis for these effects is probable.

The fact that antidiuretic substances are present in increased amounts in various edema states has been previously mentioned. Adrenal cortical insufficiency in cardiac edema has likewise been reported[23]. Adrenal cortical hormones are usually present in increased amounts in cardiac decompensation. However, they may be profoundly decreased in patients with long-standing, chronic failure in whom this continued stress causes adrenal cortical exhaustion. All of the patients with cardiac edema reported in this series had cardiac decompensation that was of long duration.

The concept that edema formation in cardiac decompensation and nephrosis is at least in part a disturbed balance of antidiuretic and diuretic factors appears sound. An increased antidiuretic effect can be produced by increased concentrations of the antidiuretic principle from the posterior pituitary. In addition a similar increased effect can be brought about by a decreased production of adrenal corticosteroids in an exhausted adrenal cortex. This would result in an unopposed antidiuretic effect of the antidiuretic hormone on the renal tubular cells. These two situations have been recognized in patients with long-standing cardiac decompensation. An antagonism between ADH and adrenal corticosteroids in their effect on water balance has also been recognized.

The sodium dilution syndrome in which the extracellular fluid space expands greatly and edema progresses rapidly is often seen terminally in patients with cardiac decompensation. Increased concentrations of ADH have been detected in the sera and urines of these patients[16,24,29,38]. Also, many have shown adrenal insufficiency. It would seem reasonable to assume that the administration of adrenal corticosteroids would counteract the excessive antidiuretic effects on the renal tubular cells present in these patients. This is precisely what occurred in the 2 patients represented by Figs. 7 and 8.

Selective diuresis of water without sodium was obtained when adrenal corticosteroids were administered. The plasma sodium as a result rose to normal concentrations. When normal concentrations of plasma sodium were obtained it is of additional interest to note that any excesses of sodium were excreted in the urine in a normal fashion. Figure 7 demonstrates that this patient while receiving cortisone was able to excrete in the urine administered excesses of sodium. This is startling when one considers that this patient was unable to remain completely edema free prior to her admission even with a low sodium intake and the use of mercurial diuretics. Apparently, adrenal corticosteroid administration restored renal ability to balance sodium and water more normally.

The mechanism as described above is, of course, in all probability too simple. The beneficial effects obtained in the majority of patients described in this report were obtained by the use of ACTH. ACTH may function to increase production of adrenal corticosteroids in a stimulated adrenal cortex or by suppressing the production

of ADH in the posterior pituitary, or both. However, ACTH has a multitude of physiologic effects, both recognized and unrecognized. Additional effects of benefit to patients with edema may be found in other actions of ACTH.

Precise criteria to be used in the selection of edematous patients for hormone therapy have not been established. Their use by us has of necessity been restricted to those patients in whom a strict anti-edema regimen has failed. The possible uses of these compounds would appear to be extensive. It is hoped that this preliminary report will cause others to share our enthusiasm, and by trial, error, and experiment determine the true place of these hormones in the management of the edematous patient.

Summary. 1. ACTH and adrenal corticosteroids have been utilized with success in the treatment of 8 patients with the nephrotic syndrome, 18 patients with refractory edema of cardiac origin, and 2 cardiac patients manifesting the sodium-dilution syndrome.

2. The use of adrenal corticosteroids in the successful management of the sodium dilution syndrome has demonstrated the probable major mechanism by which ACTH and adrenal corticosteroids exert their beneficial effect in refractory edema.

Animal experiments in the past have revealed the profound effect of adrenal corticosteroids on water metabolism. They exert a diuretic effect that opposes the antidiuretic effect of the antidiuretic hormone from the posterior pituitary gland. Refractory edema states especially those with the sodium dilution syndrome often evidence increased amounts of the antidiuretic hormone in sera and urines. Also patients with long-standing cardiac decompensation often manifest adrenal insufficiency. The administration of adrenal corticosteroids to 2 cardiac patients with the sodium dilution syndrome restored a normal water and sodium balance.

3. ACTH and adrenal corticosteroid administration often results in a return of renal tubular "sensitivity" to mercurial diuretics in patients who had previously been refractory to their use.

4. Criteria for the proper selection of patients other than refractoriness to the usual therapeutic measures have not been established. Further experience based on trial, error, and experiment will be required to determine the true value of these compounds in edema therapy.

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CORRELATION BETWEEN RENAL FUNCTION AND HISTOLOGY*

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In many instances the degree of renal dysfunction as demonstrated by function tests may not accurately reflect the extent of renal pathology. Conversely, postmortem findings frequently cannot be correlated with either the clinical or physiological findings. The opportunity to study renal pathology by means of biopsied material[2,3] soon after renal function tests are performed may help in obviating some of these discrepancies. Previous biopsy studies in hypertensive subjects undergoing sympathectomy[7] indicate a good correlation between renal arteriolar pathology and PSF excretion.

Methods. Glomerular function was estimated by using inulin clearance and tubular function by measuring the Tm for sodium para-aminohippurate[1,5]. Three periods of urine collection were made and averaged in each instance and the results corrected to a surface area of 1.73 m^2. Inulin was determined by the method of Roe, Epstein and Goldstein[4].

Biopsies were obtained within 2 to 3 days with a Turkel Needle[3] and paraffin embedded sections cut and stained with hematoxylin and eosin, and by the periodic acid (Schiff) method. The specimens so obtained measured 1 mm. in diameter and from 5 to 20 mm. long. The sections contained from 10 to 40 glomeruli and presented an adequate picture of the condition of the glomeruli, convoluted tubules, loop of Henle, interstitial tissue and the small arterioles of the cortex. These were graded as to degree of involvement from 0 to 4 plus. One plus glomerular lesions (Fig. 1) represented minimal basement membrane thickening or cellular proliferation in most glomeruli or more severe changes in occasional glomeruli. Four plus glomerular lesions (Fig. 2) represented marked thickening of the basement membrane and cell proliferation with many glomeruli being completely hyalinized. Two and three plus changes represented gradations between these two.

One plus tubular changes (Fig. 3) represented some coarse vacuolization of the cells of the convoluted tubules. Four plus tubular changes (Fig. 4) represented atrophy, marked vacuolization and cellular degeneration. Again 2 and 3 plus changes represented gradations between one and four plus.

The grading of pathological changes was done without knowledge of the results of function studies.

Results. A comparison of the histological changes seen in renal needle

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biopsy with inulin and PAH clearances and Tm_{PAH} was made in 31 instances and the data are presented in Table 1. The types of renal disease studied included acute glomerulonephritis (7 cases), chronic glomerulonephritis (8), malignant hypertension (1), nephrosclerosis (4), pyelonephritis (2), "hemoglobinuric nephrosis" (5) and intercapillary glomerulosclerosis (2). Two patients without renal disease were also studied. In 4 instances, (J.W., W.C., W.B., W.T.), patients were studied by renal biopsy and renal

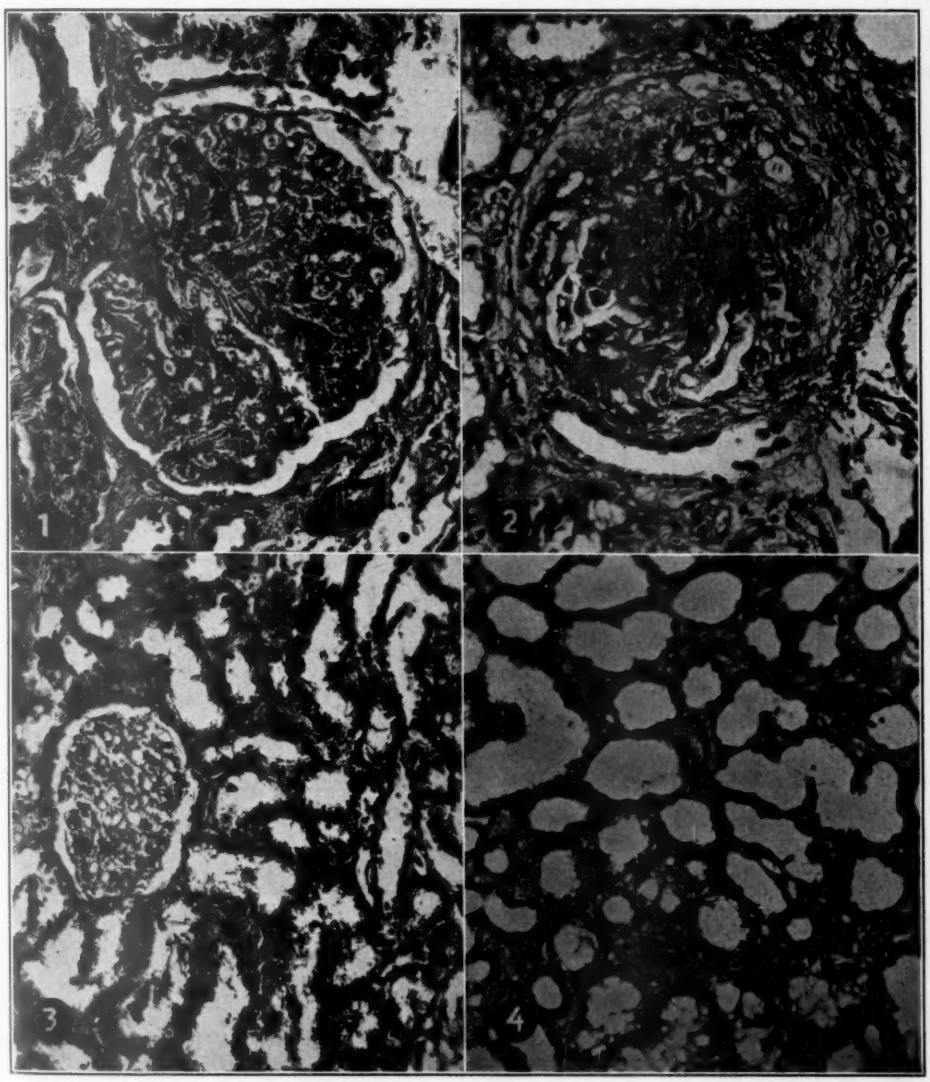

Fig. 1.—One plus glomerular pathology.
Fig. 2.—Four plus glomerular pathology.
Fig. 3.—One plus tubular pathology.
Fig. 4.—Four plus tubular pathology.

functions more than once and the intervals between these studies varied from 1 month to 1 year. Two of these were patients with glomerulonephritis, one with studies one month apart (J.W.) and one with studies one year apart (W.C.). One was a patient with "benign" nephrosclerosis who had yearly studies for 3 years (W.B.). One was a patient with a "hemoglobinuric nephrosis" who received 3 sets of studies over a period of 5 months. Comparison of glomerular pathology with inulin clearance is shown in Fig. 5. As can be seen there is only a very gross correlation. In general those with 4 plus changes had very low inulin clearances whereas those with no pathology were within the normal range for inulin clearance (131 ± 21.5 cc./min. for men)[6]. It can also be seen that patients with minimal glomerular

TABLE 1.—SUMMARY OF RENAL FUNCTION STUDIES AND ESTIMATED DEGREE OF PATHOLOGY.

				Glomeruli		*Tubules*		
Case	*Age*	*Date*	*Pathological Diagnosis*	*Clearance Inulin cc./min.*	*Degree Glomerular Pathology*	Tm_{PAH} *mg./min.*	*Degree Tubular Pathology*	*Clearance* In/Tm_{PAH}
T.M.	26	1–21–54	Normal	143	0	132	0	1.08
D.S.	25	3– 9–54	Normal	121	0	112	0	1.08
J.L.	32	10– 5–53	Acute Glomerulonephritis	109	1	59	2	1.85
R.J.	29	4–11–52	"	34	3	18	3	1.89
J.W.	28	3– 1–54	"	75	3	75	1	1.00
J.W.	28	4– 2–54	"	72	2	84	1	0.86
R.Jo.	30	4– 1–54	"	111	1	132	1	0.84
H.J.	34	4–29–54	"	138	1	126	0	1.09
F.P.	32	8–23–54	"	58	3	40	2	1.48
B.E.	45	7–30–53	Chronic glomerulonephritis	28	4	2	2	14.0
E.J.	57	7–20–53	"	39	3	41	1	0.95
W.C.	31	4– 7–53	"	8	4	0	3	..
W.C.	31	4–23–54	"	9	4	0	3	..
J.V.	64	12–17–53	"	72	1	104	1	0.69
E.S.	27	9–16–53	"	7	4	0	4	..
D.M.	56	8–18–52	"	39	2	..	1	..
W.By.	34	5–17–54	"	29	3	50	3	0.58
G.J.	58	5– 7–53	Malignant Hypertension	7	2	0	2	..
W.B.	31	5–13–52	Nephrosclerosis	101	2	37	2	2.73
W.B.	31	7– 9–53	"	130	1	104	1	1.25
W.B.	31	3– 2–54	"	131	1	110	1	1.19
N.S.	47	10–22–53	"	108	3	172	0	0.63
R.J.	30	8–27–53	Pyelonephritis	32	2	64	2	0.50
C.P.	58	6– 4–53	"	57	1	109	1	0.52
W.H.	47	2–20–53	Hemoglobinuric nephrosis	63	1	0	4	..
M.V.	47	3–24–53	"	31	1	9	4	3.54
W.T.	55	1–16–53	"	42	2	28	4	1.50
W.T.	55	2– 4–53	"	71	1	93	1	0.76
W.T.	55	4–20–53	"	82	1	80	1	1.02
L.L.	56	4– 1–52	Intercapillary glomerulosclerosis	70	3	15	2	4.66
C.T.	59	6– 7–54	"	33	3	33	2	1.00

changes (1 plus) often give low inulin clearances. In fact 6 out of 9 had inulin clearances below 100 cc./min.

Since the correlation between function and pathology might be related to the etiology of the pathology and since our largest group of patients was that with glomerulonephritis, function and pathology were compared in these (Fig. 6). This comparison shows a better correlation.

tion, it may be that this pathological finding is not functionally significant. Unlike glomerular function no particular disease appears to produce closer correlation between tubular function and histology.

High ratios of inulin clearance/Tm_{PAH} occurred in 3 instances: B.E., M.V., and L.L. Low ratios were present in R.J., C.P., W.B., J.V., and N.S., and in patient W.T. as he recovered

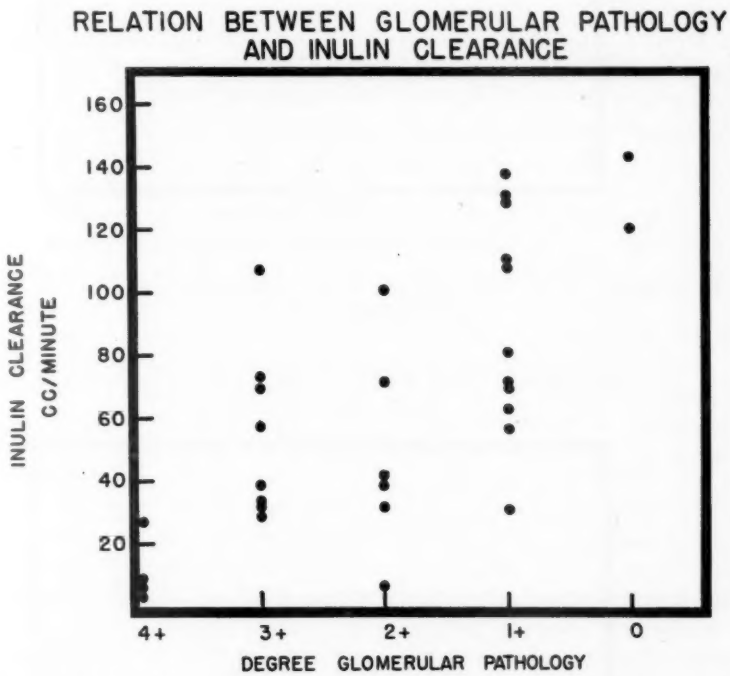

Fig. 5.—Inulin clearance plotted against the estimated glomerular pathology.

Tubular function shows somewhat better correlation with structural changes (Fig. 7). When obvious tubular damage is present (3 and 4 plus) marked depression of Tm_{PAH} occurs. With less severe damage (1 plus) 9 out of 10 patients had Tm_{PAH} values within a range accepted as normal (79.9 ± 16.7 mg./min. for men)[6]. Since tubular pathology interpreted as 1 plus changes represented vacuolization, it may be that this pathological finding is not functionally significant. Unlike glomerular function no particular disease appears to produce closer correlation between tubular function and histology.

from his "lower nephron nephrosis." These values appear to have no relationship to the etiology of the renal disease.

Since PAH extractions were not determined no interpretation of the renal plasma flows can be made.

Discussion. One of the disadvantages of needle biopsy is that the tissue obtained may not be representative of the renal pathology. In 8 instances where

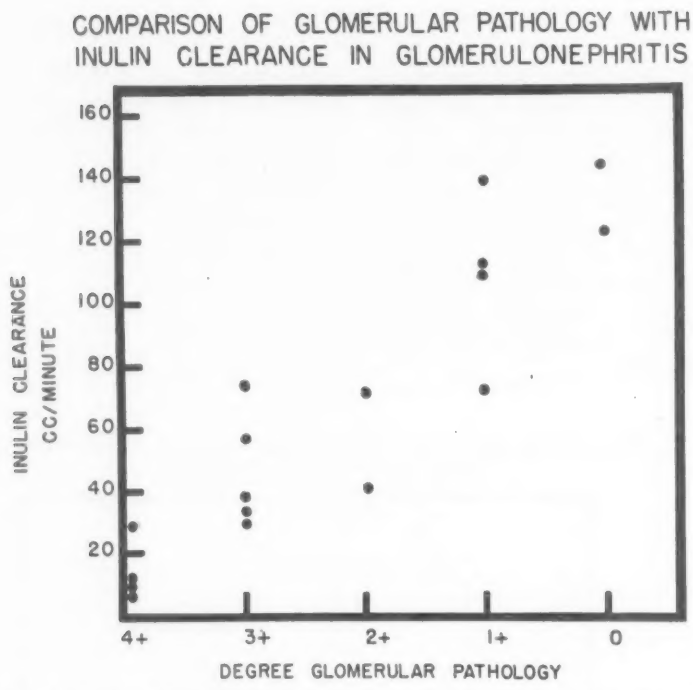

Fig. 6.—Inulin clearance plotted against the estimated glomerular pathology in patients with glomerulonephritis.

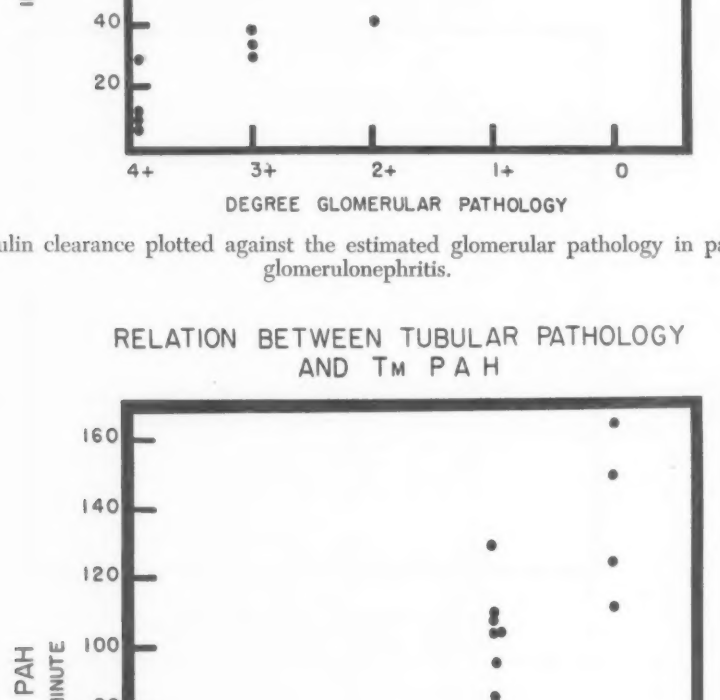

Fig. 7.—Tm_{PAH} plotted against the estimated tubular pathology.

biopsied patients subsequently came to necropsy, a comparison of the biopsy and necropsy specimens showed a similar pathological picture. It is assumed, therefore, that the specimens obtained in this study represented a fairly accurate picture of renal pathology.

The results of this study would indicate that in general there is only a rough correlation between renal function and pathology. In a specific instance, such as the comparison of glomerular function and pathology in glomerulonephritis, correlation may be better. This can probably be explained in part by the fact that glomerulonephritis is a diffuse disease, affecting all glomeruli in nearly the same degree whereas diseases such as nephrosclerosis and pyelonephritis tend to affect some parts of the kidney and spare others. Thus, the interpretation of the degree of pathological involvement is difficult, even if specimens larger than those obtained by needle biopsies were studied, and renal function may be better or worse than would be expected from the pathology present. This complicates the study of renal disease by function tests since the interpretation of the findings depends both on the etiology of the disease as well as on the degree of pathology. Hence, in glomerulonephritis, 3 plus glomerular changes give values for inulin clearance in 3 instances between 29 and 39 cc./min. but in one patient with intercapillary glomerulosclerosis and one with nephrosclerosis 3 plus glomerular changes are associated with higher clearance values (70 and 108 cc./min.).

These results also suggest that some histological changes interpreted as being pathological, such as vacuolization in the tubular epithelium may be not functionally significant or may be a normal finding. Minor changes in glomerular structure, especially thickening of the basement membrane, may, however, represent functionally significant pathology.

Summary. 1. In 31 instances renal function as measured by inulin clearance and Tm_{PAH} was compared with the renal histology as seen in needle biopsy specimens.

2. There appears to be only a rough correlation between these.

3. In glomerulonephritis there is better correlation between glomerular function and the histological changes in the glomeruli.

4. Minor histological alterations in the glomeruli are more apt to produce functional impairment than are minor histological changes in the tubules, suggesting that the former may be more important functionally than the latter.

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HORMONAL AND ELECTROLYTE INFLUENCES IN CONGESTIVE HEART FAILURE

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The pathophysiology of salt and water retention in edematous states has been the subject of numerous studies in recent years. Most investigators realize the primacy of failure of the heart in cardiac edema. It is also realized that ordinary homeostatic mechanisms, chiefly involving the kidney, become secondarily altered in congestive heart failure. The perversion of renal compensatory mechanisms results in abnormal salt and water retention.

Peters[17] stated that in congestive heart failure there is increased venous pressure and transudation of fluid resulting in hemoconcentration and renal conservation of salt and water. Verney[20] was able to show that perfusion of certain hypertonic solutions into the internal carotid artery of dogs would cause a profound antidiuresis. He attributed this to liberation of antidiuretic hormone by the osmoreceptors of the supraopticohypophyseal tract. Baldes and Smirk[1] emphasized that the acute drop in total serum solute concentration, following water ingestion, acts as the stimulus for water diuresis, rather than the absolute total serum solute concentration. Leaf and Mamby[13] then demonstrated that in hypotonic states, such as salt depleted dogs, and in occasional congestive failure patients, there is no protection from further dilution of extracellular fluid with hydration. Further dilution of serum solute did not incite a diuresis and result in a return of serum sodium and total solute concentrations to normal levels. Elkinton and Squires[7] postulated that this abnormal response of fluid retention was mediated by a reduction of circulatory volume in a critical zone of the vascular system, and was not regulated by the extracellular fluid tonicity.

There is a general tendency in edematous states towards mild hypotonicity of the extracellular fluid[15,17,19]. Administration of physiological doses of Pitressin to normal subjects and edematous patients suggests that there is very little difference in the time required to reach maximum diuresis after water loading. However, the maximal rate of urine flow is significantly lower in patients with cirrhosis and congestive heart failure after rapid intravenous infusions of hypotonic solutions[8,13,15,18]. Large doses of Pitressin have produced abnormal

water retention in patients with heart failure[11,21]. Miller[14] noted that during recovery from heart failure, with loss of edema fluid, there was a greater loss of water than of sodium in the urine. He suggested that water might be retained in excess of sodium when edema fluid accumulated.

An attempt was made in the present study to investigate the possible hormonal influences in the production of edema in congestive heart failure patients. We realize that our methods do not necessarily duplicate the sequences of the syndrome of congestive heart failure. We have chosen to study the effects of relatively large doses of Pitressin and cortisone on electrolyte and water metabolism during and in the recovery phase of edema formation induced by the administration of these hormones.

Method and Material. Five patients from the medical wards of the Philadelphia General Hospital served as subjects. These patients all demonstrated edema of cardiac origin. There was no clinical evidence of renal disease; all subjects had a normal blood urea nitrogen and were able to concentrate their urine significantly as evidenced by the total solute concentration of 600 milliosmols/liter or greater[9].* The diagnoses were as follows: two patients had inactive rheumatic heart disease, one patient had luetic aortic insufficiency, one patient had hypertensive heart disease and one patient had beriberi heart disease. The patients were maintained on digitalis and a 0.5 gm. sodium chloride diet except E.S. who did not receive digitalis, and who was allowed sodium chloride *ad libitum*. All diuretic agents were withheld during the period of these metabolic studies. The patients were allowed water *ad libitum*. Daily weight and urine volumes were recorded prior to breakfast. Blood for sodium, potassium and total serum solute determinations was drawn in the fasting state. The patients were observed during a control period of 5 to 7 days until a constant weight was maintained. Pitressin tannate in oil (5 units daily) was then injected subcutaneously each morning until the maximum effects of this hormone were established as evidenced by the rapid water retention and weight gain and subsequent stabilization of the weight at this higher level. After the weight had been constant for several days, cortisone (200 mg. orally) was administered daily, and the patient was studied during the period of further water retention. Both hormones were discontinued when maximum water and electrolyte changes, as manifested by weight gain and decreased urine volume, were established. The subjects were then observed during the period of diuresis until the weight returned to control levels. In one case (E.S.) the sequence of hormone administration was reversed. This patient received 200 mg. of cortisone daily, and then Pitressin tannate in oil until the effects of these hormones were noted. Another patient (C.B.) received Pitressin tannate in oil only and served as a control for this group.

Osmotic pressure of the blood and urine was determined by measuring the depression of the freezing point with a Beckman type thermometer, accurate to 0.001° C. The total solute concentration was expressed in milliosmols per liter. It was assumed that the solutes were totally dissociated. The total solute concentration more correctly should be expressed as millimols of sodium chloride. This value can be obtained simply by dividing the milliosmols per liter by 2.

In addition, sodium and potassium determinations of the serum and urine were performed by the flame photometer technique using a modification of the method of Overman and Davis[16].

Results. EFFECT OF PITRESSIN ADMINISTRATION ALONE. The administration of Pitressin resulted in a reduction of the urine volume and significant weight gain in all patients (Tables 1 to 5 and Figs. 1 to 4). There was an increase in the total urinary solute concentration, but the 24-hour excretion of both sodium and total solutes was increased to a lesser degree. When salt was allowed *ad libitum* (E.S.) (Table 4 and Fig. 3) the basal urinary excretion of

*Recent studies have suggested to us[9] that the ability of the patient to concentrate urine, as measured by the total urinary solute concentration, is a more accurate measurement of renal tubular function than specific gravity of the urine. Substances such as protein, sugar, urea, and others, will cause variation in specific gravity without reflecting the function of renal tubular work. These substances have a negligible effect on the osmotic pressure of the urine.

sodium was high, but there was no significantly greater increase in total solute, water, or sodium excretion than there was in the patients allowed only 0.5 gm. sodium chloride daily. All patients developed increased venous pressure, edema and weight gain when receiving Pitressin. The weight gain could not be accounted for by the small decrease in urine volume, but was ascribed to thirst and ingestion of water. Upon cessation of Pitressin, there was a diuresis within 72 hours with decrease in weight, loss of edema, rise in urinary volume and an increase of serum total solute and sodium excretion. The increase in total solute and sodium excretion tended to be a result of the increase in urine volume. There was a decrease in total urinary

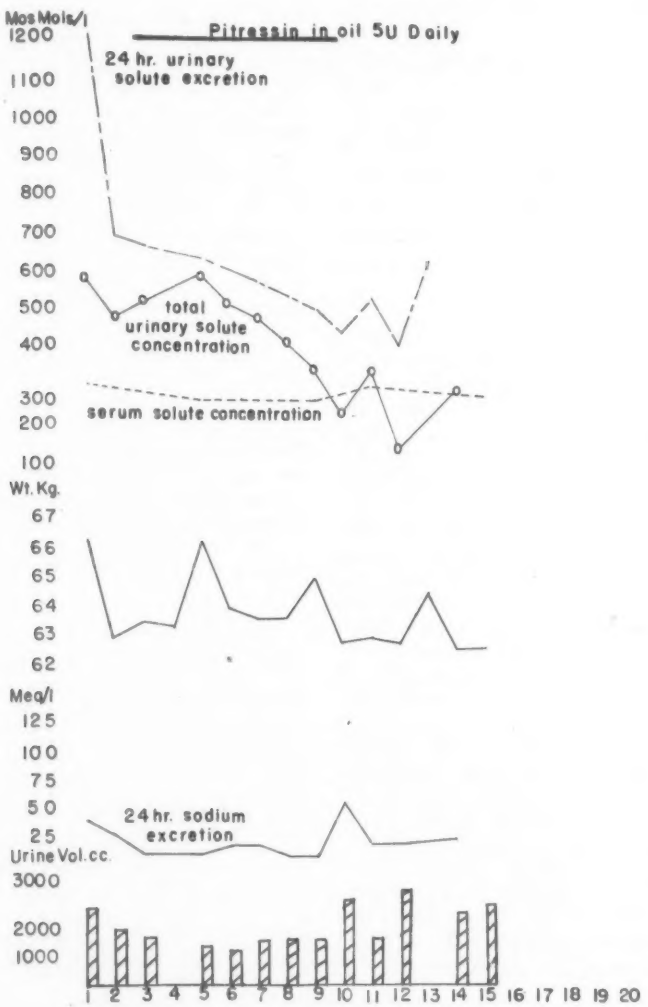

Fig. 1.—C.B. 52 C.M. Hypertensive Cardiovascular Disease. Pitressin. Administration of 5 U of Pitressin tannate in oil resulted in a reduction in urine volume. The total serum solute concentration was reduced to hypotonic levels.

solute concentration which approached isotonic values with diuresis. The serum sodium and total serum solute concentration returned to pre-treatment levels following diuresis.

EFFECT OF PITRESSIN PLUS CORTISONE. After the weight had been stabilized on 5 units of Pitressin tannate in oil, 200 mg. of cortisone was administered daily (Tables 2, 3 and 4 and Figs. 2 and 3). There was further weight gain and edema formation. The urinary excretion of solutes and sodium decreased even though urine volume remained constant or increased. This suggested that tubular reabsorption capacity for

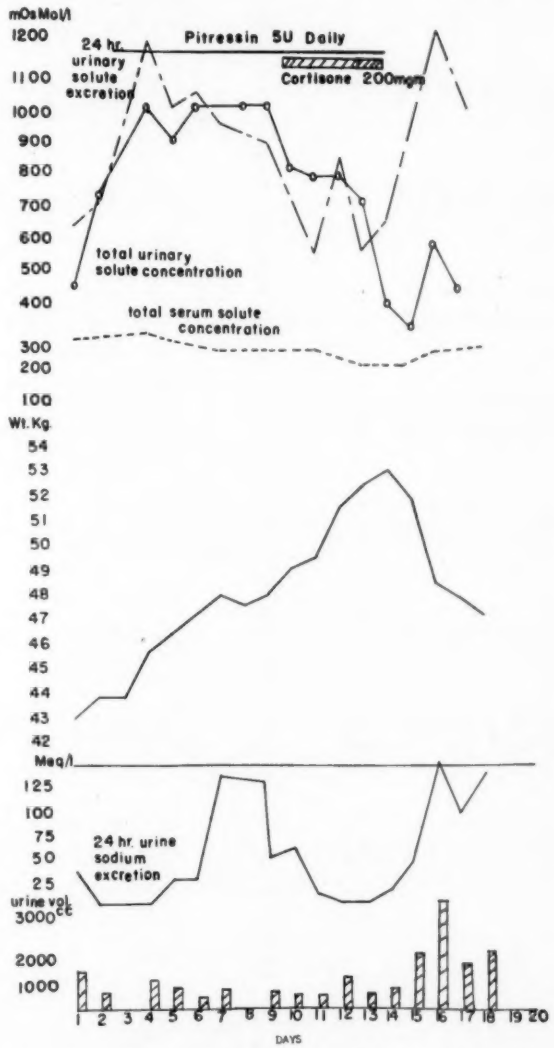

Fig. 2.—J.H. 50 W.M. Rheumatic Heart Disease. Pitressin plus Cortisone. After administration of 200 mg. per day of cortisone there was no further decrease in total serum solute concentration even though the patient continued to retain edema fluid. There was a concomitant decrease in the 24-hour sodium and total solute excretion. Total urinary solute concentration also decreased.

TABLE 1.—C. B. 52 C.M. HYPERTENSIVE CARDIOVASCULAR DISEASE. PITRESSIN

Day	Conditions	Weight kg.	24-Hour Urine Vol. cc.	Urine Sodium mEq./L.	24-Hour Excretion Urine Sodium mEq.	Urine Potassium mEq./L.	24-Hour Excretion Urine Potassium mEq.	Urine Solute m-osM./L.	24-Hour Excretion Urine Solute m-osM.	Plasma Sodium mEq./L.	Plasma Potassium mEq./L.	Plasma O.P. Solutes m-osM./L.
1		66.4	2010	19	38.4	24.9	50.4	596	1210	133	5.7	310
2		63.0	1490	20	29.8	32.1	47.9	472	704	..	..	..
3		63.6	1295	10	12.9	28.4	36.8	530	686	..	..	..
4	PTO 5U	63.4	..	..	..	..	..	..	..	..	..	..
5	↓	66.4	1090	12	13.2	30.6	33.8	602	660	130	5.2	278
6		64.0	1038	17	17.6	33.9	35.0	550	570	..	..	..
7		63.6	1250	14	17.5	36.2	38.1	477	597	..	..	..
8		63.6	1340	7.8	10.5	21.6	29.0	424	569	..	..	..
9		65.0	1350	6.6	8.9	16.4	22.2	381	515	118	4.5	275
10		62.8	2255	26.3	59.1	9.1	20.5	202	460	133	5.2	305
11		63.0	1540	9	13.8	16.3	25.1	348	536	..	..	..
12		62.8	2560	4.9	12.5	13.4	34.3	168	430	..	..	..
13		64.5	..	..	..	..	..	..	..	..	..	..
14		62.6	2055	7.5	15.4	20.1	41.2	311	639	133	7.5	298
15		62.6	2240	..	..	..	..	..	..	..	..	..

TABLE 2.—J. H. 50 W.M. RHEUMATIC HEART DISEASE. PITRESSIN AND CORTISONE

Day	Conditions	Weight kg.	24-Hour Urine Vol. cc.	Urine Sodium mEq./L.	24-Hour Excretion Urine Sodium mEq.	Urine Potassium mEq./L.	24-Hour Excretion Urine Potassium mEq.	Urine Solute m-osM./L.	24-Hour Excretion Urine Solute m-osM.	Plasma Sodium mEq./L.	Plasma Potassium mEq./L.	Plasma O.P. Solutes m-osM./L.
1		43.0	1450	27	39.2	39	56.5	488	650	131	4.8	301
2		43.9	960	11.5	11.0	36	34.6	750	720	..	..	..
3		43.9	..	..	..	..	..	..	..	..	..	..
4	PTO 5U	45.8	1175	9.9	11.7	21.7	25.5	1030	1210	140	4.1	321
5	↓	46.4	1010	30.2	33.0	24.0	26.4	924	1030	135	4.3	311
6		47.3	840	41.6	34.9	35.5	29.8	1258	1058	..	..	..
7		48.0	945	146	138	52	49.2	1031	976	128	4.1	278
8		47.8	..	..	..	..	..	..	..	..	..	279
9		48.1	900	65	59.0	66.5	59.4	1020	919	138	4.7	279
10	Cortisone	49.1	760	87.4	66.5	76.5	58.1	1018	775	..	..	..
11	200 mg. ↓	49.6	720	30	21.8	79	56.9	831	597	123	4.3	284
12		51.8	1085	134	145	79	85.6	820	889	..	..	..
13	↓	52.7	748	52	3.9	66.5	49.7	816	610	116	3.9	259
14		53.3	945	25	23.6	40	37.8	739	698	..	..	..
15		52.0	2150	29	62.4	24	51.5	392	884	..	..	..
16		48.7	4550	30.5	138.8	12.9	58.6	318	1450	138	4.3	300
17		48.0	1890	58	109.9	25	47.5	611	1150	..	..	..
18		47.3	2150	61	131.5	26.6	57.3	496	1069	137	5.2	302
19		..	..	..	..	..	..	..	..	..	..	..

TABLE 3.—J. Mc. 46 W.M. RHEUMATIC HEART DISEASE. PITRESSIN AND CORTISONE

Day	*Conditions*	*Weight kg.*	*24-Hour Urine Vol. cc.*	*Urine Sodium mEq./L.*	*24-Hour Excretion Urine Sodium mEq.*	*Urine Potassium mEq./L.*	*24-Hour Excretion Urine Potassium mEq.*	*Urine Solute m-osM./L.*	*24-Hour Excretion Urine Solute m-osM.*	*Plasma Sodium mEq./L.*	*Plasma Potassium mEq./L.*	*Plasma O.P. Solutes m-osM./L.*
1		55.9	1260	..	..	28	35.2	455	561	141	4.0	285
2		55.2	..	..	..	..	..	..	..	..	..	..
3		55.7	1870	2.4	4.5	1.1	2.1	250	467	134	4.5	..
4	PTO 5U	55.9	1430	1.0	1.0	1.5	2.1	300	431	133	4.0	267
5	Thiomerin	56.8	820	3.1	2.5	19	15.6	532	436	135	4.1	275
6	2 cc.	55.5	2020	39.0	85.9	29	63.8	379	831	..	..	..
7		55.5	..	..	..	..	..	..	..	133	4.0	267
8		55.9	688	1.9	1.3	1.8	1.2	500	344	..	..	..
9		55.9	1355	.4	.54	.5	.68	220	300	141	4.1	282
10	Cortisone	55.5	1650	1.2	1.9	5	8.3	208	342	..	..	..
11	200 mg.	56.4	790	1.3	1.1	16.4	12.9	341	277	129	4.1	300
12		57.3	940	0.9	.85	13	12.3	319	300	..	..	..
13		58.2	946	0.4	.38	7.5	7.1	321	302	135	3.9	295
14		58.2	760	5.4	4.1	13	9.9	392	299	..	..	..
15	Upper	58.2	610	46	28	34	20.6	690	410	..	..	..
16	Respiratory	58.0	948	..	..	..	..	..	..	138	3.8	314
17	Infection	57.3	..	..	..	..	..	..	..	..	..	..
18		58.4	948	7	0.6	2.2	2.08	331	313	135	4.0	285
19		58.0	1275	8	10.2	4.3	5.5	289	369	..	..	..
20		56.4	2330	57	1.73	7.1	16.6	434	1002	..	..	..

sodium had not been exceeded and that there was further conservation of sodium. The increase in weight following cortisone administration was probably secondary to sodium retention with subsequent water reabsorption[18] as there was no further dilution of extracellular fluid. Cortisone did not cause diuresis, and no antagonism between cortisone and Pitressin was noted.

EFFECT OF CORTISONE FOLLOWED BY PITRESSIN ADMINISTRATION. When cortisone was administered before Pitressin, there was weight gain without reduction in serum solute concentration or reduction in urine volume (Table 5 and Fig. 4). Urinary solute concentration and excretion remained constant. When Pitressin was added to the regimen there was the expected decrease in serum solute concentration,

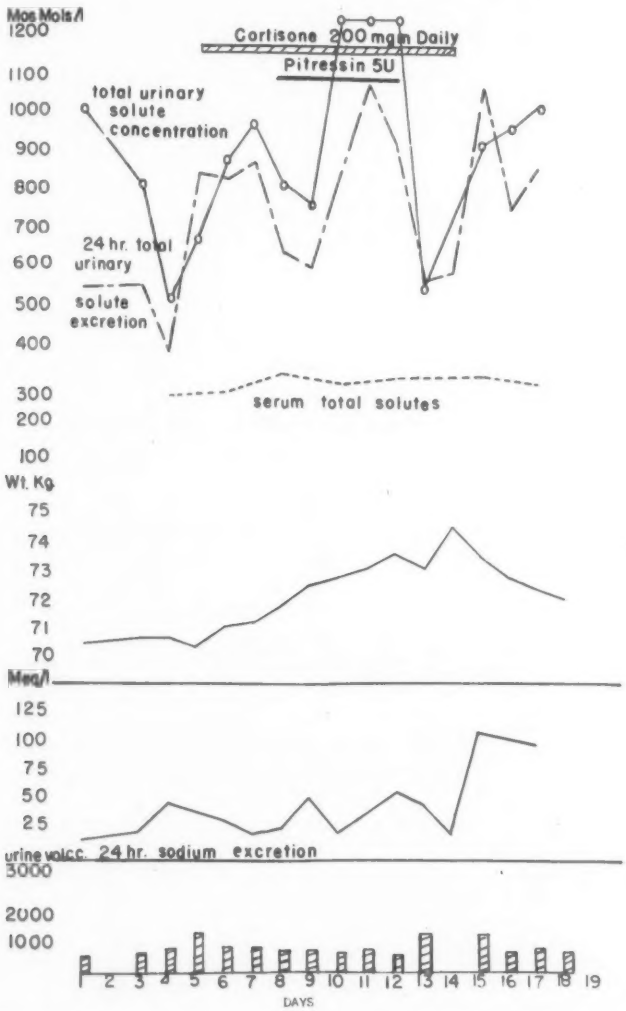

Fig. 3.—E.S. 43 C.M. Beriberi Heart Disease. Pitressin and Cortisone. Administration of 200 mg. per day of cortisone and sodium chloride *ad libitum* resulted in an increase in the basal urinary excretion of sodium. There was an increase in the total serum solute concentration with a decrease in the total urinary solute concentration.

TABLE 4.—E. S. 43 C.M. BERIBERI HEART DISEASE. PITRESSIN AND CORTISONE

Day	*Conditions*	*Weight kg.*	*24-Hour Urine Vol. cc.*	*Urine Sodium mEq./L.*	*24-Hour Excretion Urine Sodium mEq.*	*Urine Potassium mEq./L.*	*24-Hour Excretion Urine Potassium mEq.*	*Urine Solute m-osM./L.*	*24-Hour Excretion Urine Solute m-osM.*	*Plasma Sodium mEq./L.*	*Plasma Potassium mEq./L.*	*Plasma O.P. Solutes m-osM./L.*
1		58.2	1200	..	..	..	..	..	..	..	..	..
2		58.0	1030	57.6	59.4	30.2	31.5	472	485	..	..	..
3		58.0	1080	..	..	..	..	..	..	..	..	..
4		58.2	930	87.6	88.1	49.3	45.8	574	533	129	4.5	265
5		58.3	800	..	..	..	..	..	..	..	..	..
6	PTO 5U	58.2	725	..	..	..	..	..	..	..	..	..
7		58.7	740	116	85.8	60 2	44.6	837	619	..	..	..
8		59.1	..	..	..	..	..	..	..	..	..	..
9		59.6	645	..	..	..	..	890	575	..	..	..
10	Cortisone	59.6	680	70.4	47.8	100.6	69.7	1002	680	135	4.5	255
11	200 mg.	59.7	650	..	..	..	..	..	..	..	..	..
12	↓	60.5	670	..	..	..	..	970	680	..	..	..
13		60.4	1030	77.4	79.9	44.4	45.6	714	735	136.9	4.4	349
14		61.8	1080	74.1	70.1	31.4	34.0	626	670	..	..	..
15		61.9	840	76.1	64.0	9.4	7.9	492	414	..	..	..
16		61.8	1390	69.3	89.5	9.1	12.7	370	514	..	..	..
17		60.8	1810	103	184	18.0	32.5	579	1040	..	..	..
18		60.4	1480	95	141.0	27.1	40.1	626	927	134	4.4	316
19		60.4	1350	84.4	114	39.6	53.3	696	940	..	..	..
20		59.9	..	..	..	..	..	..	..	..	..	..

and there was an increase in urinary concentration and excretion of solutes. Again there was no indication of antagonism between these hormones; both were exerting different and independent actions on water and salt retention.

Discussion. Pitressin has been shown to cause water retention and weight gain in normal patients as well as in patients with edema[12]. When Pitressin was administered there was an increase in the urinary excretion of sodium and total solute with dilution of serum solutes, and decrease in serum sodium concentration. Leaf[12] suggested that if fluids were restricted at the time of Pitressin administration these changes would not occur. The weight gain and dilution of extracellular fluid resulted from an increased ingestion of water, suggesting that the mechanisms for

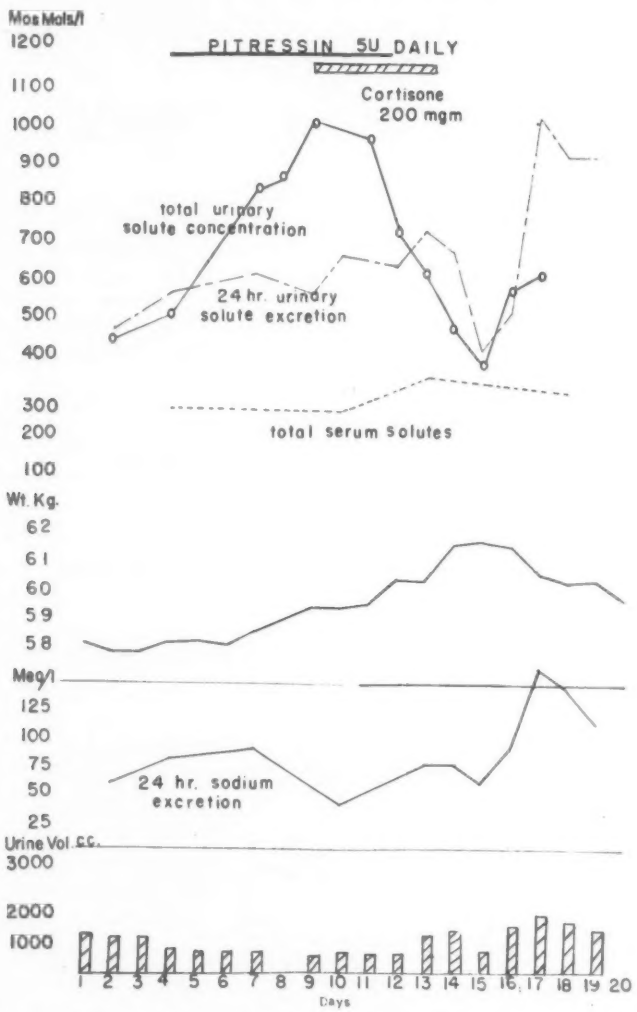

Fig. 4.—J.H. 57 C.M. Luetic Heart Disease. Cortisone plus Pitressin. In this study cortisone was administered before Pitressin. Upon the addition of Pitressin tannate in oil the urinary solute concentration and excretion tended to increase. There was no reduction in serum solute concentration or urine volume.

TABLE 5.—J. H. 57 C.M. LUETIC HEART DISEASE. CORTISONE AND PITRESSIN

Day	*Conditions*	*Weight kg.*	*24-Hour Urine Vol. cc.*	*Urine Sodium mEq./L.*	*24-Hour Excretion Urine Sodium mEq.*	*Urine Potassium mEq./L.*	*24-Hour Excretion Urine Potassium mEq.*	*Urine Solute m-osM./L.*	*24-Hour Excretion Urine Solute m-osM.*	*Plasma Sodium mEq./L.*	*Plasma Potassium mEq./L.*	*Plasma O.P. Solutes m-osM./L.*
1		70.5	560	18.8	10.6	28.1	15.7	1011	563	..	..	..
2		..	..	..	..	..	..	..	..	..	..	..
3		70.7	700	30.8	21.6	27.0	18.9	815	511	..	..	..
4		70.7	750	60.7	45.6	30.2	22.7	520	390	137.8	5.2	295
5		70.4	1240	9.7	12.2	43.8	54.4	696	864	..	..	..
6	Cortisone	71.1	930	35.4	32.9	54.3	50.4	885	823	139.1	5.0	299
7	200 mg.	71.3	890	25.1	22.3	71.7	63.8	982	873	..	..	..
8		71.9	785	31.4	24.6	62.5	44.0	830	651	137	4.6	320
9	PTO 5U	72.5	790	63.4	50.0	33.8	26.7	773	609	..	..	..
10		72.9	685	20.2	14.0	48.1	32.9	1261	866	141.9	4.7	306
11		73.2	870	44.8	39.0	58.9	51.3	1263	1090	..	..	..
12		73.6	740	74.2	55.0	56.6	41.9	1261	933	153.7	4.8	324
13		73.2	1010	41.9	42.4	52.5	53.0	556	572	..	..	..
14		74.5	..	58.1	..	57.5	..	1425	..	..	..	..
15		73.4	1110	96.1	106	31.0	34.2	993	1099	144.2	5.1	334
16		72.9	800	..	..	..	..	986	789	..	..	..
17		72.4	880	103.5	91.1	35.9	31.6	1050	925	153.7	4.8	315
18		72.1	700	..	..	..	..	..	..	..	..	..

preservation of the normal serum solute concentration and urinary excretion of water and solutes were operating to produce edema. Exogenous antidiuretic factors caused further dilution of the carefully guarded extracellular fluid tonicity at a time when elaboration of a hypotonic urine of low sodium concentration could have corrected this hypotonic state of the serum. The continued reabsorption of water by the kidney under these conditions leads to the perversion of a homeostatic mechanism with consequent edema formation. Antidiuretic substances have been isolated from the blood and urine of patients with congestive heart failure[2,6]. Large doses of Pitressin tannate in oil have caused marked weight gain and abnormal responses to intravenous infusions of water[3]. Increased sensitivity to the antidiuretic substances is probably not the cause for this abnormal response. Both normal patients and those with edema and ascites diurese in a normal period of time after physiological doses of Pitressin in response to water loading[11,12,18,21,22]. Likewise, abnormal inactivation of physiological amounts of exogenous Pitressin does not occur because there is an equal duration of response to this hormone in both the normal and edematous groups[3,15,22]. Increased production of antidiuretic substances for prolonged periods of time, irrespective of total serum concentrations, or inability to inactivate abnormally high concentrations of these antidiuretic substances, or both, must be considered as possible mechanisms.

A large body of evidence exists demonstrating antagonism between the posterior pituitary and the adrenal cortex in salt and water metabolism. These effects have been demonstrated in both adrenalectomized and hypophysectomized animals[4,5,8,10]. Attempts to cause diuresis with adrenal cortical substances have failed in most instances. Corticoids at least fail to correct the water loading diuretic inadequacy of edematous patients or the abnormal weight gain and edema caused by exogenous administration of Pitressin[11,16].

The additional weight gain following cortisone administration, after stabilization on 5 units of Pitressin tannate in oil daily, occurred with a decrease in total solute and sodium excretions after the addition of cortisone. When cortisone was administered initially there was no change in the serum sodium and solute concentration during the period of weight gain and edema formation. There was no dilution of serum solutes until Pitressin was administered. This would indicate that Pitressin and cortisone have separate and distinct actions on fluid retention. Pitressin administration caused a retention of water without retention of total solutes or sodium, whereas cortisone caused a reduction in the urinary excretion of sodium (the most active osmotic constituent of the serum and urine), and subsequent obligatory water reabsorption. This would suggest that water can be reabsorbed without sodium, whereas sodium reabsorption would entail water being carried with it. There was no decrease in either sodium or total solute excretion after the administration of Pitressin. However, weight gain, venous distention, and edema ensued with subsequent hypotonicity of the serum suggesting that these changes were independent of sodium retention. Cortisone addition caused still further weight gain and edema with a decrease in urinary excretion of sodium and total solutes. Thus with cortisone administration, water and sodium were reabsorbed in what we presume to be isotonic proportions.

Upon the withdrawal of Pitressin there was a drop in the total urinary solute and sodium concentrations with elaboration of a hypotonic urine of large volume. The urinary loss of sodium and total solutes was far less than could be accounted for by the loss of extracellular fluid of isotonic concentrations, and would indicate that more water than sodium was excreted during this recovery phase of congestive failure.

The hypotonicity of the serum under the influence of Pitressin was probably not due to an intracellular shift of sodium. If this had occurred, one would have expected either an increase in serum potassium concentration or an increase in the urinary excretion of potassium. During these studies there was no significant change in the serum concentration or urinary excretion of potassium. Furthermore, the decrease in total serum solute and sodium concentrations was accompanied by significant weight gain.

The homeostatic mechanism for preservation of the circulating blood volume probably includes both adrenal and posterior pituitary influences. These hormones may operate independently to produce sodium and fluid retention with subsequent congestive heart failure.

Summary and Conclusions. 1. The administration of Pitressin tannate in oil for prolonged periods of time to cardiac patients resulted in the production of a picture of congestive heart failure with venous distention, edema and weight gain. There was an increase in urinary total solute and sodium excretion with a reduction of the serum solute and sodium concentration. Weight gain could not be accounted for by the decrease in urine volume and was ascribed to thirst and subsequent ingestion of water.

2. Upon cessation of Pitressin there was loss of weight and edema fluid. The serum sodium and total solute concentrations returned to pretreatment levels with the development of a dilute urine of large volume. Again the urinary total solute and sodium concentrations were far less than would be expected if extracellular fluid was excreted in isotonic concentrations.

3. The administration of cortisone after weight stabilization had been attained with Pitressin caused further edema and weight gain. There was, however, no further decrease in the total serum solutes and sodium concentrations in the face of water retention. This would entail at least two separate mechanisms, namely, (1) retention of water due to Pitressin, and (2) sodium retention due to cortisone followed by water retention.

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THE RELATIONSHIP OF PREDOMINANCE OF LESIONS IN THE RIGHT VERSUS THE LEFT LUNG TO THE PROGNOSIS OF ADVANCED PULMONARY TUBERCULOSIS BEFORE CHEMOTHERAPY*†

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A RETROSPECTIVE analysis of 1504 patients admitted to Trudeau Sanatorium from 1930 to 1939, with active, advanced pulmonary tuberculosis without major tuberculous or nontuberculous complications, has recently been completed. The materials, methods and background features of the series are described elsewhere[8].

Comparisons and evaluations were made in two ways:

a) FIVE-YEAR RESULT. The 5-year result was considered "good" if the disease had become clinically controlled, with no evidence of cavity and with negative sputum, within 3 years; and if relapse had not occurred within the balance of the 5-year period. If a patient was lost through death from nontuberculous causes or loss of contact in less than 5 years, the case was rated "nonevaluable." Otherwise the result was "poor."

Sixty-seven moderately advanced and 8 far advanced cases were "nonevaluable," leaving 1,429 cases for analysis by this method.

b) THE 20-YEAR TUBERCULOSIS MORBIDITY AND MORTALITY experience was corrected for differences in duration of observation by the life table method. Patients were classified as "sick" in a given year if under treatment for tuberculosis or known to have positive sputum during six or more months of the year. Proportions of "well," "sick" and "dead-tuberculosis" were computed after elimination of lost cases at the time the loss occurred.

Differences in proportions were tested for statistical significance by the standard error and chi square methods. A difference which might have arisen from chance alone in no more than 2% of cases was considered significant. All differences which failed to meet this criterion were rated as nonsignificant, even though in many instances they may have been indicative of possible or even likely interdependence of the developments being tested.

The cases were analyzed by all factors which could be determined in retrospect, including the presence and amount of disease in each lung separately according to a method described by Salkin and Cadden[10].

Results. The 5-year results showed a surprising but not statistically significant difference in favor of left versus right sided, *far advanced* disease (Fig. 1). No such difference was discernible by this method of evaluation when the disease was moderately advanced in extent.

The 20-year morbidity and mortality experience was then studied. In Figs. 2 and 3 it is seen that patients with far advanced disease in the left lung and moderately advanced, minimal or none

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†Presented at the 14th Veterans Administration-Army-Navy Conference on Chemotherapy of Tuberculosis, February 7, 1955, Atlanta, Georgia.

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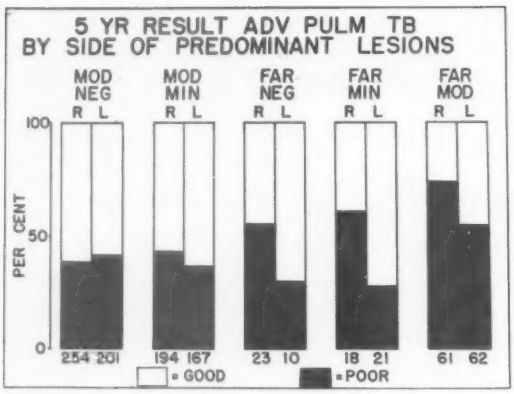

Fig. 1

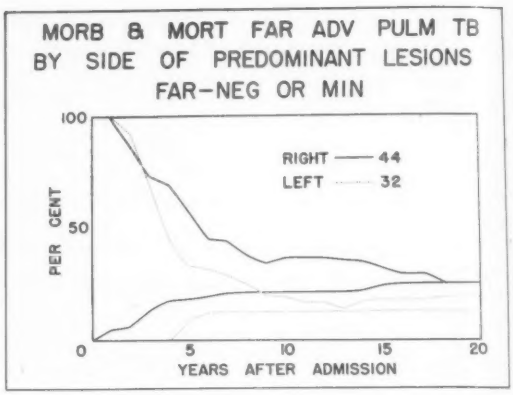

Fig. 2

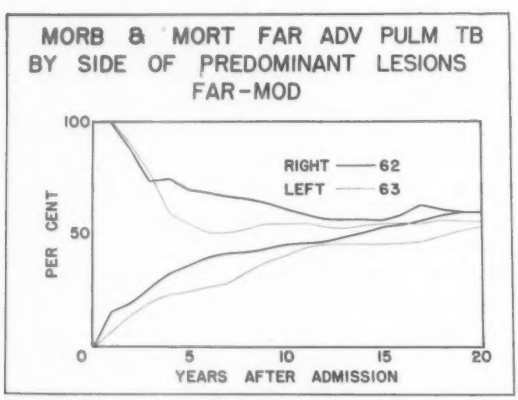

Fig. 3

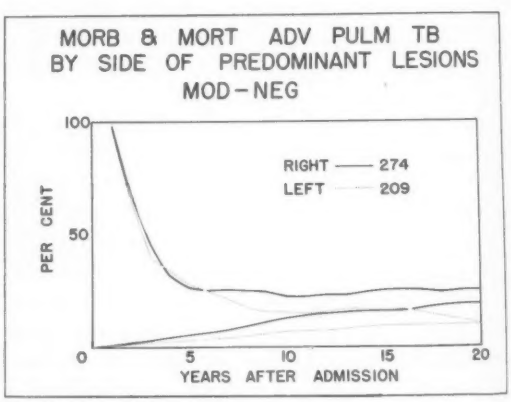

Fig. 4

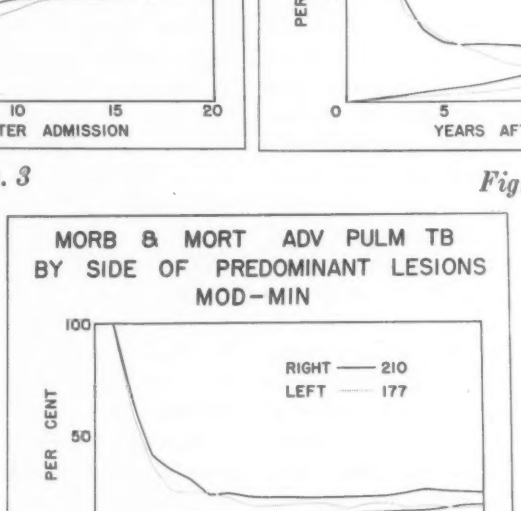

Fig. 5

Figs. 1 to 5.—Legends on opposite page.

in the right, fare better in the long run than those patients with disease of comparable extent predominantly on the right. Differences were tested at the 5, 10 and 15-year levels. The differences were statistically significant at only one point, at 10 years, in Fig. 3.

In Figs. 4 and 5 it may be seen in addition that patients with moderately advanced disease in the left lung and minimal or none in the right fare better than patients with moderately advanced disease in the right and minimal or none in the left. None of these differences were statistically significant.

Comment. A glance at the charts will show that the trend is overwhelmingly in the direction of favoring the left lung. It is more noticeable in those cases with disease almost or entirely in one lung (Figs. 2 and 4) than in those with a somewhat more equal distribution (Figs. 3 and 5). This fact, the remarkable consistency of the trend favoring the left lung, is not taken into consideration by chi square or standard error tests for statistical significance.

However, it almost certainly lends weight to the hypothesis that left lung tuberculosis behaves more favorably than right lung tuberculosis, especially in the absence of any plausible contrary explanation of the manifest trend. These observations should be interpreted with caution because this was not a controlled study and one cannot be sure that age and character and even extent of disease may not have been more favorable in the left than in the right lung lesions. This possibility is slightly increased by the fact that the right lung is slightly larger than the left. However, it is not likely that there were major differences.

The findings suggest that the human handles tuberculosis in the right lung less effectively than it handles a comparable amount of disease in the left lung. To the writer's knowledge there have been two previous suggestions that this may be so. Left pneumothorax was once thought to be more effective than right pneumothorax[6]. Dock[3] has endeavored to explain apical localization of tuberculosis on the peculiarities of pulmonary circulation and upon the oxygen and carbon dioxide requirements[1,4] of *M. tuberculosis* on growth. Starting with about 20 mm. of mercury, the head of hydrostatic pressure in the pulmonary artery is presumed to approach zero in the erect position, in the upper lungs, thus permitting an abnormal accumulation of oxygen and an abormal removal of carbon dioxide from normally ventilated areas, thus creating an environment particularly favorable to the growth of tubercle bacilli. Because of the two angles in the right pulmonary artery, not present in the left pulmonary artery, Dock[2] postulates a pre-

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Fig. 1.—Five-year results in advanced pulmonary tuberculosis by side and extent of predominant lesions.

Fig. 2.—Morbidity and mortality of pulmonary tuberculosis, far advanced in one lung and minimal or none in other, by side of predominant lesions.

Fig. 3.—Morbidity and mortality of pulmonary tuberculosis, far advanced in one lung and moderately advanced in the other, by side of predominant lesions.

Fig. 4.—Morbidity and mortality of pulmonary tuberculosis, moderately advanced in one lung and none seen in the other, by side of predominant lesions.

Fig. 5.—Morbidity and mortality of pulmonary tuberculosis, moderately advanced in one lung and minimal in the other, by side of predominant lesions.

sumed greater loss of hydrostatic pressure on the right than on the left due to the turbulence of flow around corners. This may cause a zone of high alveolar oxygen and low carbon dioxide, resulting from deficient or absent pulmonary circulation, to extend from the apex more deeply on the right than on the left. The pulmonary circulation in the upper lobes has not been actually measured, to the writer's knowledge. Martin and Cline[7], however, have recently verified the postural changes in both O_2 and CO_2 tensions in upper lobe air spaces of humans by catheterizing the upper lobe bronchi. Scott, Hanlon, Olson and associates[5,9,11] have also apparently demonstrated by anastomosis and ligation of branches of the pulmonary arteries in monkeys the adverse effect of purely systemic arterial blood upon tuberculosis, administered intravenously both before and after operation.

It is of considerable practical importance that the 5-year results (Fig. 1) gave an incomplete story with particular regard to moderately advanced disease in contrast to the long term morbidity and mortality data which are presumed to give a more reliable picture of the situation.

Summary and Conclusions. Of 1,504 consecutive patients admitted to Trudeau Sanatorium, 1930 to 1939, with advanced pulmonary tuberculosis without major complications, over 90% were followed to death or 1953 to 1954. Among various factors studied was the predominance of lesions in the right versus the left lungs. Correcting roughly for differences in extent of disease, the tuberculosis morbidity and mortality experience for the next 20 years was consistently more favorable in those patients whose lesions were predominant in the left lung than in those with predominantly right lung disease. A possible physiologic and anatomic explanation for this finding is discussed.

ADDENDUM: A slight difference in morbidity and mortality favoring left lung lesions has been found upon review of 478 patients with *unilateral minimal* disease (Mitchell, R. S.: Am. Rev. Tuberc., **67**, 401, 1953).

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HEMOGLOBIN C DISEASE IN IDENTICAL TWINS*

By Robert D. Lange, M.D.**

and

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Hemoglobin C disease is an hereditary hemolytic anemia due to the presence of the abnormal hemoglobin, C, in the homozygous state. This entity was first described in 1953[14,22]. Hemoglobin C disease has an estimated incidence of 1 per 6,000 Negroes[26] and approximately 21 cases have so far been recognized. This report presents for the first time the clinical and laboratory findings of hemoglobin C disease in identical twins. In addition to the identification of the hemoglobin by paper electrophoresis, red cell survival studies were carried out by the radioactive chromium method.

Methods. The electrophoretic studies were performed according to the method of Motulsky, Paul and Durrum[12], but with 8 to 11% oxyhemoglobin solutions. Approximately 0.01 cc. amounts of the solutions were streaked on Whatman #3 MM filter paper strips and the paper was placed on a frame with the ends immersed in veronal buffer at pH 8.6 and ionic strength of 0.05. The buffer was contained in a plexiglass cell which had been divided into compartments. The current was run at 1.4 milliamperes per strip with a voltage of 150 to 160 for 5 hours.

The cell survival studies were performed with the patients' cells and with normal cells which were incubated *in vitro* for one hour at room temperature with $Na_2 Cr^{51} O_4$ solution[6,24,27]. Ascorbic acid was added[16] and the cells were then injected into the subjects. The radioactivity of serial blood samples was measured in a well type scintillation counter† and the counts were corrected for radioactivity decay and hematocrit variations. The initial count was taken as the 100% value. The average red cell life figures were obtained by the method of Dornhorst[5] and were corrected for a Cr^{51} elution of 1% per day. Fecal urobilinogen was determined by the method of Schwartz and associates[18] and fetal hemoglobin by the method of Singer[21]. The red cell osmotic fragility studies were performed by the method of Suess *et al.*[25]. The remaining laboratory tests were performed by standard methods.

Case Reports. The subjects, R.O'N. and D.O'N., were 25-year-old Negro males who were found, on routine preemployment examination, to have enlarged spleens and mild anemia. The patients had been completely asymptomatic and throughout their high school and college careers had engaged in vigorous contact athletics. In childhood both had suffered from asthma but had otherwise been well.

Physical examinations revealed no abnormalities except for splenic enlargement.

The patients' mother was 53 years old and the father 58. The father had been treated for a neurologic disorder in 1950 and 1951. His hemoglobin at that time was 15.4 and 15.8 gm. per

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†The facilities of the Radioisotope Unit of the Minneapolis Veterans Administration Hospital were used for these measurements.

100 cc. of blood on repeated determinations. The mother had always been well. The patients had two brothers and three sisters all of whom had been well. Routine blood studies on one brother (J.O'N.) revealed a normal hemogram. However, his red cells sickled in a bisulfite test[3]. Electrophoretic studies revealed the presence in those cells of sickle cell hemoglobin and normal adult hemoglobin (Fig. 3). The results of these studies confirmed a clinical diagnosis of sickle cell trait. Following the completion of the studies reported in this paper, one of us (R.D.L.) had the opportunity to study two of the sisters. One sister was found to have hemoglobin C disease. The other sister was found to be heterozygous with normal adult hemoglobin being present in addition to hemoglobin C in her red cells.

Laboratory studies on the identical twins are summarized in Table 1. The anemia, which was present in each during part of the 5-month period of observation, was normocytic, normochromic in character. Persistent reticulocytosis and increased fecal urobilinogen excretion indicated increased hemolysis. Fetal hemoglobin determinations were performed on several occasions with varying results. As seen in Table 1 some of the determinations were elevated above 1.2%, the highest value for normal controls in this laboratory. Sickling tests by the bisulfite method[3] were consistently negative. Figure 1 shows the numerous target cells seen in peripheral blood smears of R.O'N. The red cells also showed moderate anisocytosis, some poikilocytosis and occasional nucleated red cells. D.O'N.'s peripheral blood smear was similar. Table 2 shows the decreased osmotic fragility of the red cells of both, in comparison with normal cells.

As shown in Table 3 both brothers had identical blood group factors.* This observation lends credence to the belief that the subjects were identical twins. Further support for this belief came from comparison of the skull roentgenograms of the two subjects. Although no abnormality was revealed in either film the comment on the skull markings was as follows: "The skull markings are peculiarly similar

TABLE 1.—LABORATORY STUDIES ON IDENTICAL TWINS WITH HEMOGLOBIN C DISEASE

	R.O'N.	*D.O'N.*
R.B.C.	5,150,000 per μl	4,560,000 per μl
Hemoglobin	11.9 to 15.0 gm/100 cc. bld	12.9 to 16.1 gm/100 cc. bld
Hematocrit	35.6 to 42%	36.9 to 45%
M.C.V.	82 c.μ.	89 c.μ.
M.C.H.	27.5 $\gamma\gamma$	32 $\gamma\gamma$
M.C.H.C.	34%	36.5%
Reticulocytes	3.6 to 9.7%	4.0 to 8.9%
Fecal Urobilinogen	524 to 1,649 (mg/day)	619 to 1,780 (mg/day)
Fetal Hgb.	0.61 to 3.7%*	0.70 to 3.7%*
Sickling	Negative	Negative
W.B.C.	9,500	10,750
Neutrophils	68	71
Lymphocytes	22	19
Monocytes	10	5
Eosinophils	0	4
Basophils	0	1

* One determination at the Army Medical Service Graduate School Department of Hematology, Walter Reed Army Medical Center showed 2.9% on each. We are indebted to Lt. Col. J. H. Akeroyd for performing this determination and the electrophoretic patterns on the two sisters.

TABLE 2.—ERYTHROCYTE OSMOTIC FRAGILITY IN HEMOGLOBIN C DISEASE

Na Cl %	*Control* (% *Hem.*)	*R.O'N.* (% *Hem.*)	*D.O'N.* (% *Hem.*)
.60	0	0	0
.54	0	0	0
.51	2	0	0
.48	6	0	0
.45	29	0	0.9
.42	74	0.9	9
.36	93	9	16
.33	93	9	43
.27	96	33	54
0	100	100	100

*The blood groupings were performed by Dr. Philip Levine, Ortho Research Foundation, Raritan, New Jersey.

. . . and suggest the possibility that these (subjects) are identical twins."

Figure 2 shows the results of the red cell survival studies. The patient's own cells in each instance, tagged by

TABLE 3.—BLOOD GROUPING IN IDENTICAL TWINS WITH HEMOGLOBIN C DISEASE

	D	*C*	*E*	*c*		*Jk*^{a}	*Fy*^{a}	*Le*^{a}		
R.O'N.	O	+	+	o	+	M	o	o	o	kk	Ss
D.O'N.	O	+	+	o	+	M	o	o	o	kk	Ss

The hemoglobin paper electrophoretic patterns of the two subjects, R. O'N. and D.O'N. as well as that of the brother, J.O"N., are shown in Fig. 3. For comparison the patterns of normal adult hemoglobin (Hgb A) and sickle cell hemoglobin (Hgb S) are illustrated. It should be noted that hemoglobin A had the fastest mobility and hemoglobin C the slowest, while hemoglobin S had an intermediate mobility. That the twins were truly homozygous for hemoglobin C was demonstrated by the absence of other hemoglobins in the electrophoretic pattern.

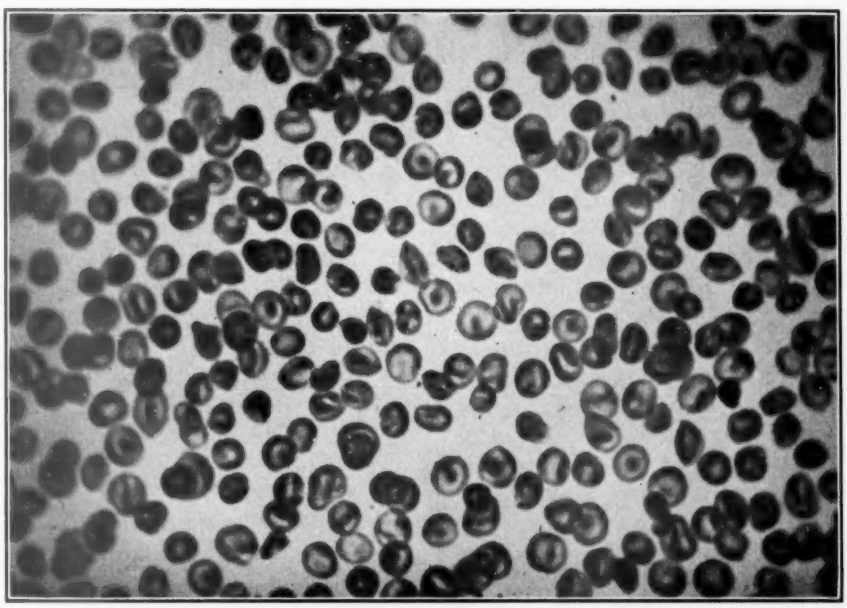

Fig. 1.—Peripheral blood of R.O'N., showing presence of numerous target cells.

in vitro incubation with Cr^{51}, showed markedly shortened survival. The average life of the cells was calculated as 21 and 24 days for R.O'N. and D.O'N., respectively. On the other hand, transfused radiochromium-tagged normal cells had normal survival in D.O'N., while in R.O'N. the normal cells had a normal survival for 2 weeks followed by a rapid disappearance coincident with a febrile illness. These comparative red cell survival studies demonstrated a primary red cell defect in the patients' cells.

Discussion. At the present time 8 species of hemoglobin have been described[1,7,8,9,13,19] and a system of nomenclature has been accepted[23]. Two of these, hemoglobin A and hemoglobin F (normal fetal hemoglobin), are normal varieties. Hemoglobins C, D, E, G, H and S are abnormal adult hemoglobins. The clinical states as-

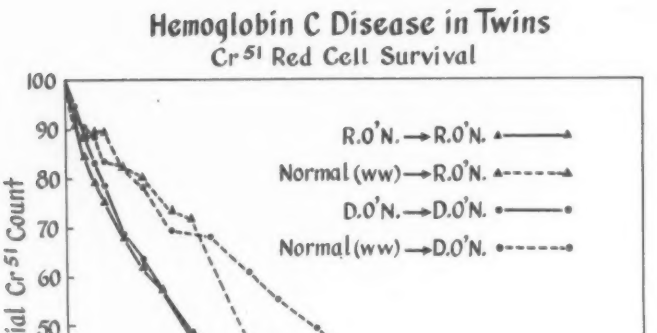

Fig. 2.—Erythrocyte survival studies in subjects, R.O'N. and D.O'N.

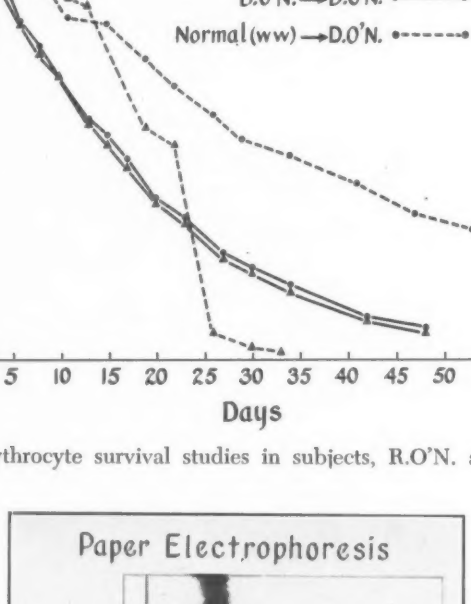

Fig. 3.—Hemoglobin patterns of identical twins, R.O'N. and D.O'N., and a brother, J.O'N. Normal hemoglobin (A) and sickle cell hemoglobin (S) are shown for comparison.

sociated with abnormal hemoglobins are named in the following manner. Individuals homozygous for the abnormal hemoglobin or having two abnormal hemoglobins, or having an abnormal hemoglobin in combination with another inherited red cell abnormality are classified as having the disease. Individuals possessing normal hemoglobin together with an abnormal hemoglobin are classified as having the trait.

Hemoglobin C was first described in 1950 in combination with hemoglobin A and in combination with hemoglobin S[10]. In 1953, hemoglobin C was first reported in the homozygous state[14,22]. Terry, Motulsky and Rath[26] reviewed the reported cases of hemoglobin C disease and added one of their own. Singer *et al.*[20] have recently reported 4 more cases.

The present cases are similar to those previously described. So far, all other known cases except one have been in Negroes. The one exception was reported in a 16-year-old boy of Italian parentage[4]. In common with the others, our patients had excessive hemolysis. There was reticulocytosis and increased fecal urobilinogen excretion. Numerous target cells were present on peripheral blood smear and sickling tests were negative. As in other cases the red cells had decreased osmotic fragility. The electrophoretic patterns, necessary to confirm the diagnosis, showed the presence of only the abnormal hemoglobin C. Although on most determinations the fetal hemoglobin values were within normal limits, other determinations showed elevated values in contrast to previously described cases[20,26]. However, at least one other observer has found an elevated fetal hemoglobin value in hemoglobin C disease[2]. Red cell survival studies demonstrated a shortened life span due to an intracorpuscular defect. The average red cell life figures of 21 and 24 days of autotransfused cells in our subjects are comparable with an uncorrected "half life" of 19 days in one other patient[28]. On the other hand, in 4 other subjects, the average red cell life, determined by the Ashby technique when patients' cells were tranfused into normal individuals, was found to be 13 days, about 30 days, 42 days, and 55 days, respectively[20,17,26,22].

Some of the other cases of hemoglobin C disease have had arthralgia but this symptom was lacking in our patients.

It is of interest that one of the brothers of our patients was found to have sickle cell trait with a hemoglobin pattern of SA, and one of the sisters was found to have hemoglobin C trait with a hemoglobin pattern of CA. These findings, together with the presence of homozygous C hemoglobin in 3 family members, would indicate, therefore, that the parents, if they become available for study, should show a hemoglobin pattern of SC and AC since hemoglobin C is apparently inherited as a Mendelian dominant[11,14,15,17,20,22,26].

Summary. The case histories and laboratory findings of hemoglobin C disease in identical Negro twins have been presented.

The diagnosis may be suspected by the presence of splenomegaly, anemia, reticulocytosis, numerous target cells and absence of sickling, but electrophoretic studies are essential for confirmation.

Red cell survival studies showed a markedly shortened survival time of autotransfused cells, indicating the presence of a hemolytic process.

From a clinical point of view, in our subjects hemoglobin C disease was an apparently benign condition.

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CLINICAL STUDIES ON A VASOPRESSOR AGENT: METARAMINOL (ARAMINE)*

I. OBSERVATIONS IN NORMOTENSIVE SUBJECTS

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In 1910, Barger and Dale[1] described a group of "sympathomimetic" compounds, and set forth certain basic principles governing the relationship of molecular structure to their pharmacological activity. Beta-phenylethylamine is the structural nucleus of the group which includes epinephrine as its prototype, and the closely related compounds, ephedrine, phenylephrine (Neosynephrine) and amphetamine (Benzedrine). Minor modification of structure permits a wide selection of related pharmaceutical actions. The structurual relationship of epinephrine, norepinephrine (Levophed) and metaraminol is shown in Fig. 1.

For clinical purposes, it is desirable to select a pressor drug, which approaches an ideal, from the large number of sympathomimetic agents that have been synthesized. Interest in such an agent was stimulated because of the apparent increase in shock due to bacterial infections in the clinics associated with the University of Minnesota[14]. In describing the properties of the more desirable pressor agent, Hellerstein[4] has stated: ". . . (it) would elevate blood pressure, increase peripheral resistance, produce a proportionate increase of coronary flow, have minimal side effects, and would not decrease cardiac output or produce serious arrhythmias." To these attributes we would add the following: The agent should exert a prompt pressor effect after administration; it should be possible to control readily the resulting pressor effect; reactive hypotension (secondary vasodilation) should be absent or minimal; the drug should be available for administration by convenient routes and preferably without fluid vehicle for intravenous use; it should be free from tachyphylactic activity (diminishing response with successive administrations); the pressor drug should cause minimal renal vascular constriction; and finally, the agent should not provoke local tissue damage at the sites of injection.

It is unlikely that any one agent will meet all of the desirable requisites. Available information suggested, however, that metaraminol might approxi-

*levo-l-(m-hydroxphenyl)-2-amino-1-propanol

Metaraminol was generously supplied by Dr. John Beem, Asst. Medical Director, Sharp & Dohme, West Point, Pa.

mate the ideal agent more closely than other commonly used drugs. Livesay *et al.*[6] characterized metaraminol as a potent vasopressor agent having the advantages of prolonged duration of action, causing no detrimental alterations in cardiac rhythm, and having no appreciable effect on cardiac output. Sarnoff[11] demonstrated in dogs an increase in myocardial contractility and cardiac output following the administration of small doses of metaraminol. blood pressure is elevated from marked hypotensive to normotensive ranges with norepinephrine or metaraminol, however, Moyer *et al.*[8] found that cerebral blood flow is increased. Livesay[6] and Moyer[7] compared renal blood flow following the administration of norepinephrine and metaraminol. In comparison with the magnitude of the pressor response, less renal vascular constriction was noted for metaraminol than for norepinephrine. Metaraminol may

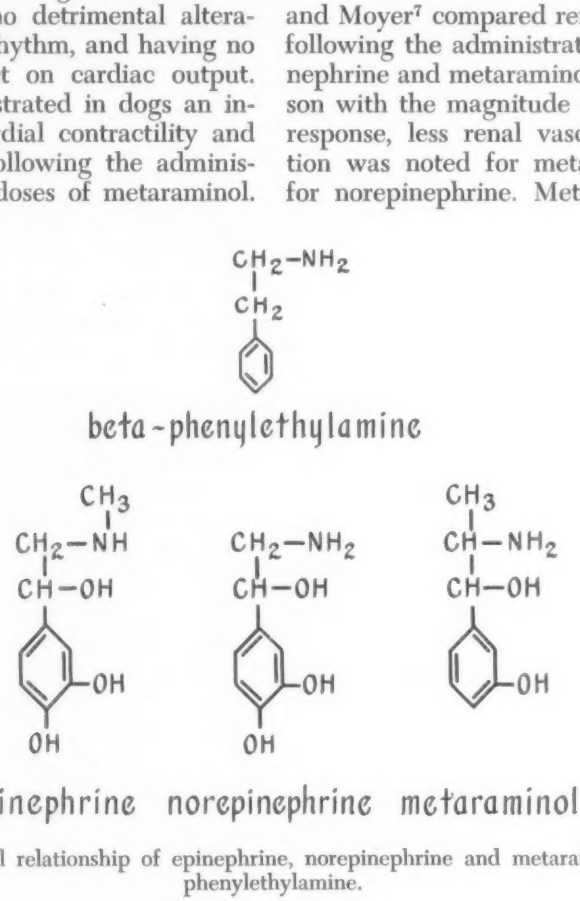

Fig. 1.—Chemical relationship of epinephrine, norepinephrine and metaraminol to beta-phenylethylamine.

This cardiotonic action, which preceded the vasopressor effect, occurred independently of coronary blood flow. However, larger doses did result in an increase in peripheral resistance and coronary blood flow. Sarnoff regards the central or cardiac effect of the pressor amines of equal or greater importance than the peripheral action in the treatment of shock. Elevation of blood pressure in normotensive patients decreases cerebral blood flow. When be given by any parenteral route. It does not cause tachyphylaxis[10].

Norepinephrine, though the most potent of the available pressor agents, has a serious disadvantage because it causes local tissue damage at the site of injection. It has been reported that local venospasm and blanching of the skin occurs in nearly half of the patients treated with this drug[5]. The procedure of a "surgical cut-down" with insertion of a polyethylene catheter

does not afford complete assurance against tissue necrosis or thrombophlebitis. Deep ulceration involving skin and subcutaneous tissue has required skin grafting and even amputation[12]. Precautions undertaken for the protection of local tissue result in a delay of therapy. The injection of undiluted norepinephrine must be avoided and a fluid vehicle is required for its administration. Only the intravenous route of administration is recommended. Preliminary catheterization of the vein, careful attention to the adjacent tissues, and the constant supervision by nursing personnel have been enforced whenever norepinephrine has been used at the University of Minnesota Hospitals. In spite of these precautions, serious damage to the tissues, thrombosis, and cellulitis have followed its use. After 14 days of continuous therapy, in a patient recently observed, extensive gangrenous sloughs occurred. This constant threat of tissue damage due to norepinephrine is particularly disconcerting in patients being treated for shock due to bacteremia. These patients have been observed to survive if the blood pressure is supported over long periods of time, sometimes exceeding 2 weeks[13].

Both methoxamine (Vasoxyl) and mephentermine (Wyamine) leave much to be desired in the treatment of shock because the pressor response to these agents is lost relatively early in the course of therapy[2,3]. Phenylephrine has the disadvantage of causing cardiac arrhythmia[9].

In an effort to evaluate further the clinical values of metaraminol, the present study was undertaken. Because of the difficulty in interpreting observations made during the state of shock in human beings, observations were made initially on normotensive volunteers.

Methods of Study. Single subcutaneous, intramuscular, or intravenous injections of metaraminol were administered on 51 occasions to 31 subjects. All of the volunteers were young normotensive males free of demonstrable cardiovascular disease. Before injection, the individuals were instructed and encouraged to report all subjective effects that followed. The blood pressures were measured with a standard clinical sphygmomanometer with the patients in the supine position. The pulse was evaluated by palpation of the radial artery. Subcutaneous injections were made into the volar surface of the forearm, and intramuscular injections into the deltoid muscle. Intravenous injections were given into the antecubital vein. After a period of rest, and following 2 control readings before administration of the drug, blood pressures and the pulse were measured at 1 to 5-minute intervals shortly after the injections, and 5 to 15 minutes in instances where the drug caused a prolonged effect. The injection sites were examined during and after each study, and all objective and subjective observations were recorded.

Comparative studies were possible in 15 subjects, each of whom was tested by both subcutaneous and intramuscular injections of metaraminol on different days. The cardiac rhythm was also studied electrocardiographically in 14 individuals.

Results. PRESSOR RESPONSE. Only a slight rise in blood pressure occurred following either the subcutaneous or intramuscular injection of 5 mg. of metaraminol. However, a dose of 7 to 10 mg. caused a more marked and reproducible increase in both systolic and diastolic pressures. As a baseline for determining the pressor effect with respect to its onset and duration, arbitrary values were selected, consisting of a rise of 20 mm. above the systolic baseline and a rise of 10 mm. above the diastolic baseline blood pressure. There were individual variations in relation to the rapidity of the rise in pressure and the maximal response. The duration of the elevation also varied from subject to subject. Following subcutaneous and intramuscular injections, a significant pressor effect, once obtained, almost always persisted for 30 minutes.

On the other hand, an occasional volunteer displayed a significant response for as long as 3 hours.

The results are summarized in Table 1 and illustrated in Fig. 2. A single subcutaneous or intramuscular dose had a latent period of 5 to 12 minutes before a rise in pressure was detected. Maximum blood pressure readings occurred approximately 30 minutes after injection. Pressor effects persisted for 50 to 90 minutes after injection. The rapidity of onset and the duration of a maximum response were correlated with an increase in dose. A finding not anticipated was a more prolonged and at least equally potent pressor response that followed the subcutaneous injections as compared to the intramuscular injections. This was also noted in the comparative subcutaneous-intramuscular studies of the 14 paired observations

TABLE 1.—AVERAGE DURATION AND INTENSITY OF PRESSOR EFFECT OF METARAMINOL IN NORMOTENSIVE VOLUNTEERS FOR THE DOSES AND ROUTES SHOWN

Number of Individuals	*Route of Administration*	*Dose in mg.*	*Onset of Pressor Effect**	*Time of Maximum Response**	*Duration of Response**	*Maximum Systolic Rise (mm. Hg)*	*Maximum Diastolic Rise (mm. Hg)*	*No Pressor Response*
4	Intramuscular	5	10	30	63	52	36	2
4	Subcutaneous	5	18	30	44.5	35	10	2
10	Intramuscular	7 to 8	12.3	26.2	54.5	50	22	1
11	Subcutaneous	7 to 8	9.6	35	71.7	51	24	1
4	Intramuscular	10	6.5	29	68	70	46	0
6	Subcutaneous	10	5.3	29.3	90.3	88	35	0
12	Intravenous	3 to 6	1.7	4.7	25.1	66	31	0

* Time in each case refers to minutes after injection.

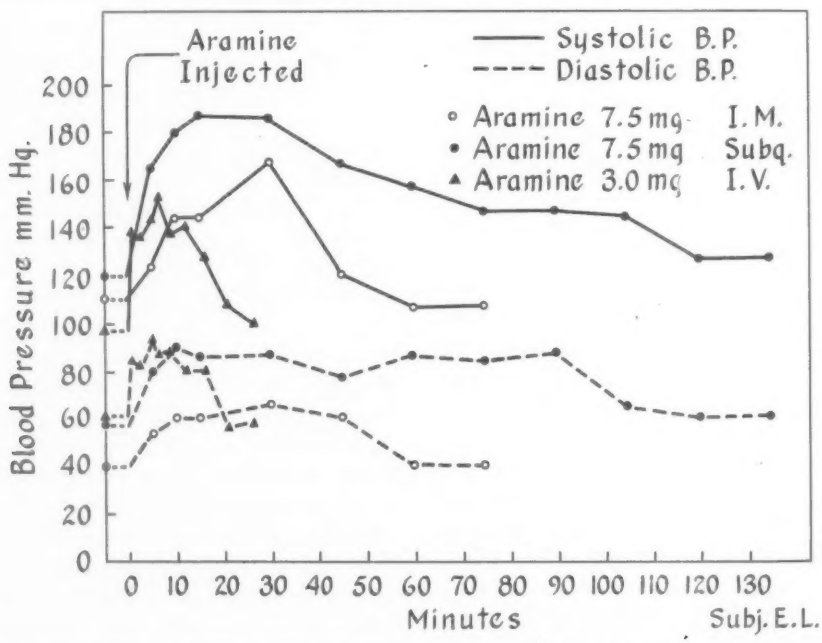

Fig. 2.—Comparative effects of subcutaneous, intramuscular and intravenous administration of metaraminol (Aramine).

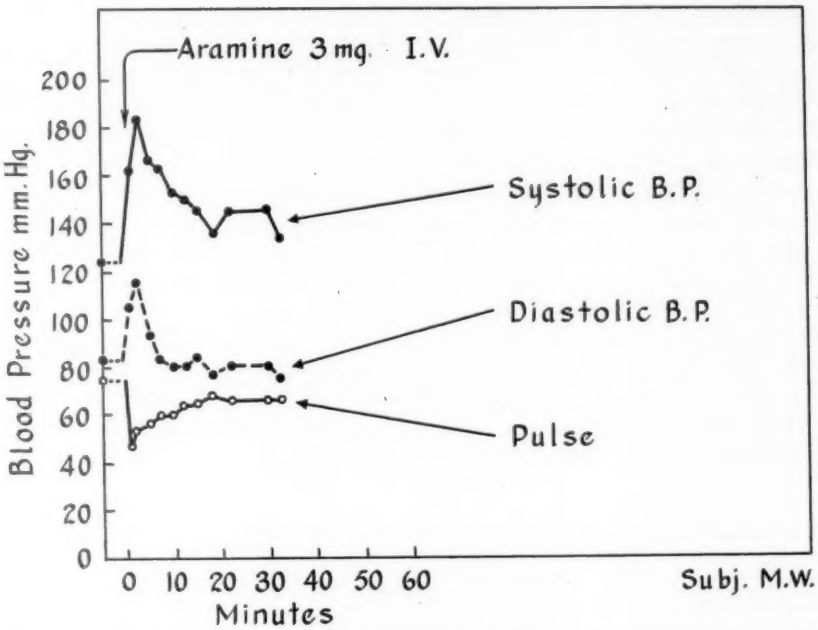

Fig. 3.—Blood pressure and pulse response following intravenous injection of metaraminol (Aramine).

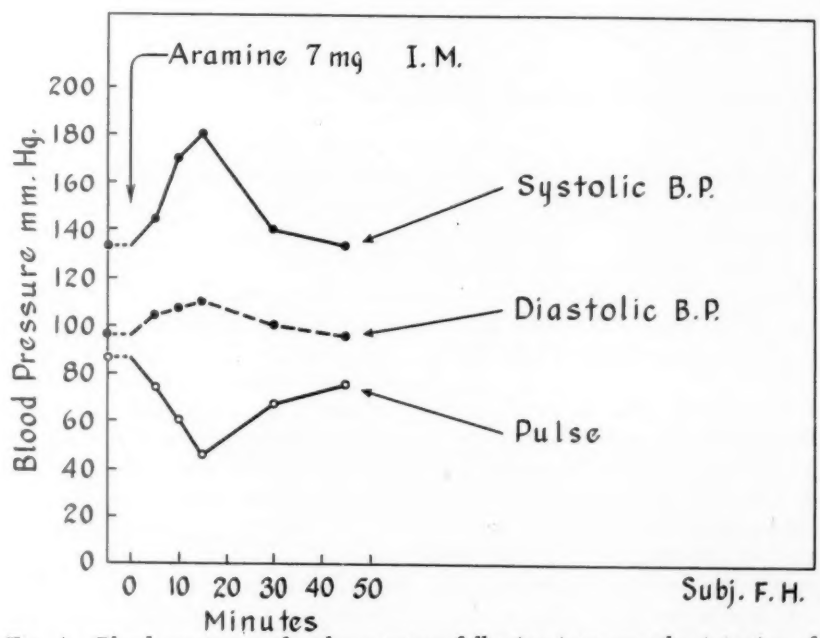

Fig. 4.—Blood pressure and pulse response following intramuscular injection of metaraminol (Aramine).

in which the same doses were used; 11 demonstrated a superior response to the subcutaneous administration.

Following the intravenous injection of metaraminol, a pressor response occurred within 2 minutes (Figs. 2 and 3). While a maximum pressor effect was manifested within 5 minutes, a protracted response was observed for an average of 25 minutes.

PULSE AND ELECTROCARDIOGRAPHIC STUDIES. A slowing of pulse rate (of 10 or more per minute) occurred in 36 of the 51 individuals (Table 2). The decrease in the rate was noted particularly after metaraminol was given intramuscularly (Fig. 4). A pressor response without a decrease in pulse rate occurred frequently, whereas only an occasional subject had a significant slowing of the pulse without an elevation in blood pressure. A reciprocal relationship between blood pressure and pulse was observed (Figs. 3 and 4).

Sinus arrhythmia was detected electrocardiographically in 5 of 14 control tracings. Following the injection of metaraminol, 13 of 14 subjects manifested sinus arrhythmia. There was a close time relationship between the appearance of the pressor response, the maximum blood pressure reading, and the onset and marked manifestations of arrhythmia. Changes in auricular conduction were reflected by a slight shortening of the PR interval and flattening of the P waves (Fig. 5). Flattening of the P wave was particularly prominent after a long diastole. Nodal rhythm or nodal escape occurred in 4 subjects. A changing auricular pacemaker was observed on one occasion (Fig. 6). No abnormality of ventricular rhythm or conduction was noted. Of interest was the disappearance of occasional premature ventricular contractions in one subject after metaraminol had been given intravenously.

SIDE EFFECTS. Commonly encountered reactions were severe occipital headache and a compressive sensation in the chest (Table 3). Nausea and vomiting occurred occasionally. These manifestations were always related to an excessive elevation of blood pressure. The symptoms subsided promptly following a decline in blood pressure and were relieved when the blood pressure was reduced by changing the subject's position from supine to sitting. Irregularities of pulse were clarified with the aid of electrocardiograms and were, as noted above, sinus or auricular in origin. Diaphoresis, persisting up to 3 hours after injection, was observed in 7 patients. The injections were not generally considered to be painful and careful examination of the site of in-

TABLE 2.—PULSE CHANGES FOLLOWING ADMINISTRATION OF METARAMINOL TO VOLUNTEERS FOR THE DOSES AND ROUTES SHOWN

Number of Individuals	*Route of Administration*	*Dose in mg.*	*Time of Onset of Slowing**	*Time of Maximum Slowing**	*Duration of Slow Rate**	*Decline in Beat per Minute*	*No Pulse Response*
4	Intramuscular	5	35	61.2	65	15	1
4	Subcutaneous	5	25	47.3	60	20	1
10	Intramuscular	7 to 8	11	39	66	23	2
11	Subcutaneous	7 to 8	19.5	38	62.5	21	1
4	Intramuscular	10	17.5	52.5	157	26	2
6	Subcutaneous	10	37.5	50.1	100.8	27	1
12	Intravenous	3 to 6	3.2	4.6	10.8	18	7

* Time in each case refers to minutes after injection.

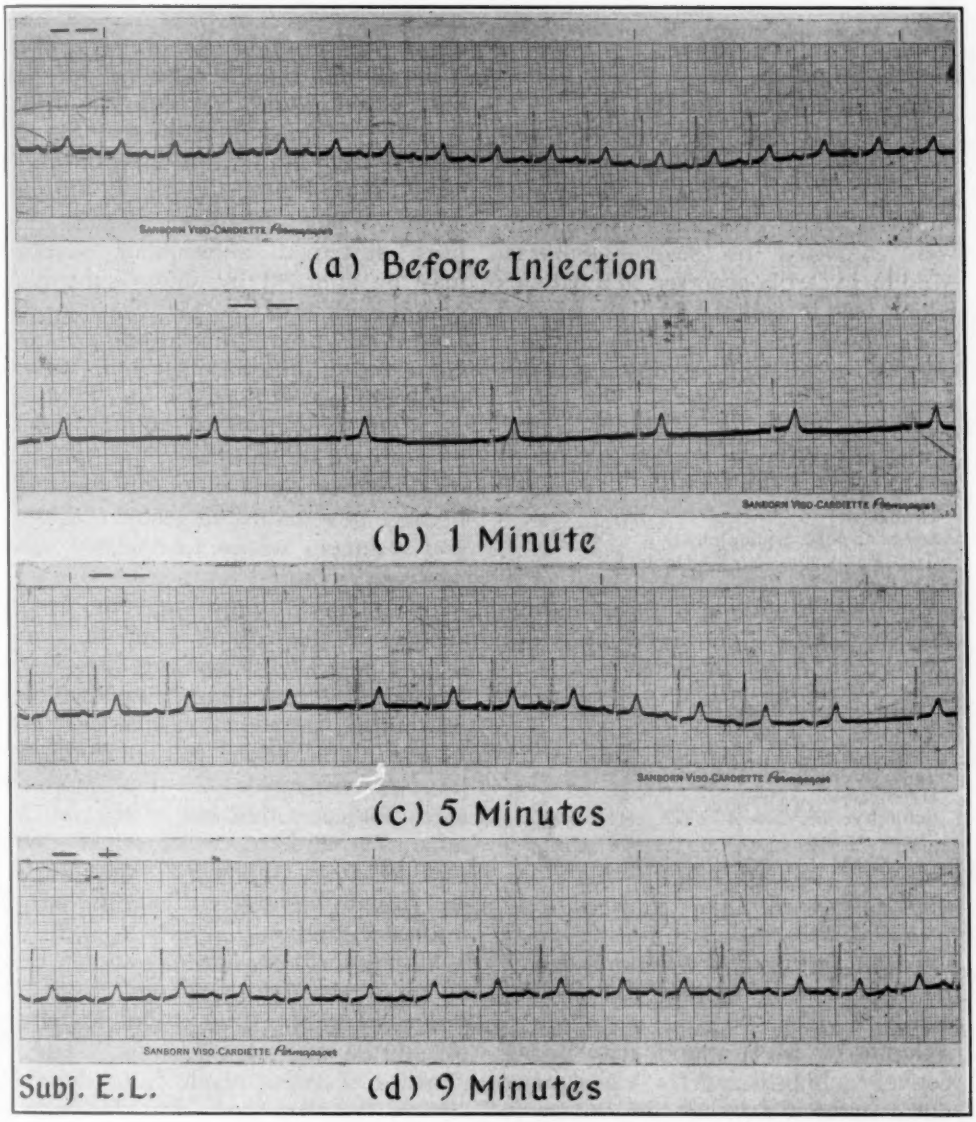

Fig. 5.—Electrocardiographic sequence following administration of 3 mg. metaraminol intravenously to normotensive volunteer (all lead 2).

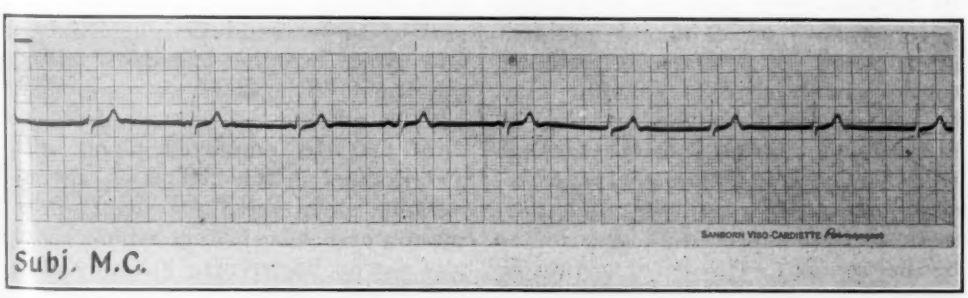

Fig. 6.—Changing auricular pacemaker in the presence of bradycardia after administration of 7 mg. metaraminol.

jection failed to reveal injury to the skin or underlying tissues.

A "warm feeling" was associated with diaphoresis. After the rapid intravenous injection of metaraminol, a feeling of euphoria and "tingling throughout" were reported by several subjects. Mild tachycardia occurred in 2 patients which was in contrast to the expected sinus slowing otherwise observed. In 2 subjects, mild and asymptomatic hypotension lasting 2 to 4 hours followed the hypertension induced by metaraminol.

TABLE 3.—SIDE EFFECTS AFTER ADMINISTRATION OF METARAMINOL TO FIFTY-ONE VOLUNTEERS

Headache	14
Irregular pulse (asymptomatic)	14
Transient compressive feeling in chest	8
Diaphoresis	7
Painful injection site	6
Nausea	5
"Warm" feeling	5
Dizzy "high" feeling	4
"Heart beats fast"	4
"Tingling throughout"	3
Vomiting	2
Chill	2
Tachycardia (asymptomatic)	2
Hypotension (asymptomatic)	2
Subjective shortness of breath	2
"Cold" feeling	1
Tachypnea	1
Transient erythematous rash	1
Urinary frequency	1

Comment. Metaraminol may be effectively administered by 3 parenteral routes without demonstrable injury to tissues at the site of injection. A prompt and potent vasopressor response may be obtained with a single intravenous injection of 3 to 10 mg. A problem often posed by patients in profound shock, namely, venous collapse, may be circumvented by the injection of metaraminol directly into the femoral vein. This vein is almost always accessible, and a time-consuming and traumatic cut-down procedure may thereby be avoided. The ensuing pressor response improves venous tone so that a needle can then be inserted into an antecubital vein. Subsequent maintenance of blood pressure may be secured by the intravenous infusion of 30 to 200 mg. of metaraminol per liter of fluid[13]. When the blood pressure has been sustained, subsequent support may be afforded by single subcutaneous injections of the drug. Since a prolonged effect may be achieved by subcutaneous or intramuscular injections of metaraminol, it becomes practical to maintain blood pressure by intermittent injection. This has been particularly useful where fluids had to be curtailed because of renal insufficiency or in several instances where vasopressor support was required for periods exceeding one week[13]. Injections given at intervals of one-half to 2 hours place less of a strain on nursing personnel. Technical disadvantages incident to continuous intravenous infusions are avoided. The lack of patient cooperation is circumvented. The present study indicates that use of the subcutaneous route achieves an equally potent and more prolonged action and is therefore to be preferred over the intramuscular route.

Metaraminol provokes a variable but at times intense vagotonic effect. In this respect, the drug resembles phenylephrine and methoxamine[9]. Irregularities of pulse result from depression of the sinus node and depression of auricular conduction. In shock, slowing of the heart rate may be undesirable when increased cardiac output is needed to maintain peripheral blood flow. Since atropine effectively blocks the vagal effect of these compounds without altering the pressor effect, the drug may be employed along with metaraminol in selected cases. In one instance; metaraminol produced a pressor response in a patient whose shock was due to bacteremia, but only after the bradycardia was abolished by

atropine. In another instance, metaraminol was given to a patient with supraventricular tachycardia. A 2:1 block with an auricular rate in excess of 300 was increased to 3:1 and 4:1 blocks with effective ventricular slowing. Freedom from ventricular arrhythmia is reassuring. Livesay's[6] impression that metaraminol demonstrates no detrimental arrhythmias is in accord with the findings in the present study.

No significant toxic effects were correlated with metaraminol directly. The conditions of the experiment were such that acute hypertension was induced with consequent headache, nausea, and vomiting in several subjects. Diaphoresis, with a cold moist skin not unlike that of vasomotor collapse, was the only definite side effect and this caused no discomfort.

Summary and Conclusions. Single injections of metaraminol (Aramine) were given to normotensive subjects in a preliminary clinical study of this new vasopressor agent. As far as the present observations permit, the drug is a potent pressor agent and is nontoxic. Its potential clinical value is reflected in its safety with respect to tissue at the site of injection and its prolonged effect. The availability of an effective pressor agent for intravenous and subcutaneous use offers certain medical and nursing advantages in the care of patients in shock.

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NONSPECIFIC HEMAGGLUTINATION INHIBITING FACTOR IN HUMAN SERUM*

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In 1952, in a study of the hemagglutination test for tuberculosis of Middlebrook and Dubos in ocular disease we[1] noted that in 5 cases of sarcoidosis the hemagglutination test showed no antibody titer. That the skin of patients with sarcoid does not respond usually to large doses of tuberculin, even after repeated inoculations with B.C.G. vaccine is well known and this has been thought by some to be a specific "anergy" to tuberculin. Friou[3] studied intracutaneous reactions to trichophytin, mumps and tuberculin antigens in patients with sarcoidosis and suggested that the decrease in delayed hypersensitive reactions is a broad, immunologically nonspecific, phenomenon probably affecting all delayed hypersensitive reactions.

In 1949, Wells and Wylie[6], demonstrated that a tuberculin neutralizing substance is present in the gamma globulin fraction of the sera of patients with sarcoid. They mixed serum of sarcoid patients with old tuberculin and allowed the mixture to stand for 48 hours. They then injected a small amount of the mixture intracutaneously into persons who were known positive tuberculin reactors and found that no skin reaction now occurred. Control sera from healthy patients usually had no such effect on the tuberculin test. They found that though the sera from established cases of sarcoidosis are by far the most constant in the tuberculin neutralizing effect, the phenomenon is occasionally observed with apparently normal sera and in diseases other than sarcoidosis. Conversely, the serum from an occasional patient with sarcoidosis did not neutralize O.T. They concluded that this test involving the injection of material from the patient into another person was not suitable as a diagnostic procedure.

We decided to determine (1) whether this tuberculin neutralizing factor of Wells and Wylie would also neutralize the O.T. antigen of the hemagglutination test of Middlebrook and Dubos, and (2) whether it was present in a high percentage of sarcoid sera as contrasted with other sera. This would transfer the reaction to the test tube and it could then conceivably be valuable as a diagnostic test for sarcoid.

Following the method of Wells and Wylie, sera from patients with sarcoid-

*This study was aided by the Milton Berle Fight for Sight Award of the National Council to Combat Blindness.

osis was mixed with the 4 × O.T. antigen which is used in the hemagglutination test and the mixture was allowed to stand for 48 hours. Using this mixture as the modified O.T. antigen, the Middlebrook-Dubos hemagglutination test was performed with sera of tuberculous patients known to have positive hemagglutination reactions in high titer to the unmodified O.T. antigen. Sera from other sick hospital patients and from healthy individuals were also tested in the same way as were the sera of patients with sarcoid.

Methods and Materials. There were 386 tests performed on a total of 121 individuals. The antigen after having been treated by the serum of a given individual was always used in at least two tests with the sera of two or more high titer tuberculous patients. Sarcoid patients' sera were tested against 4 or 5 high titer sera.

Sera from 13 patients with sarcoidosis, 16 patients with pulmonary tuberculosis, 15 hospital patients with a variety of chronic illnesses other than sarcoidosis or tuberculosis, (Fig. 4), and 74 healthy controls were tested. Most of the healthy controls were also hospital patients who had no obvious inflammatory or degenerative disease, but who had come to the hospital for some elective operation such as hernioplasty or plastic surgery. The rest of the healthy controls were laboratory technicians and doctors.

Definitions. The term "test serum" is used in this report to describe the serum which is being tested for its inhibiting effect upon the hemagglutination reaction using an "indicator serum."

The term "indicator serum" is used to describe a serum with a known constant high titer of antibodies in the hemagglutination test of Middlebrook-Dubos.

Procedures. Test serum is inactivated at 56° C. for ½ hour. Two cc. inactivated serum, 3.3 cc. saline buffered to pH 7.4, plus 2 cc. 1:1000 Merthiolate is incubated at room temperature with 0.6 cc. 4 × O.T.* for 48 hours (two hours at 37° is also satisfactory and then Merthiolate may be omitted). The above concentrations were found to be optimal. One-tenth cubic centimeter packed washed sheep cells is added and incubated at 37° C. for two hours. Cells are washed 3 times with buffered saline and then suspended in 50 cc. buffered saline. This suspension of cells treated as described above is the antigen sensitized cell system to be reacted with test sera. These cells are tested against known high titer "indicator sera" to determine the inhibiting effect of test sera.

An O.T. sensitized cell system is prepared similarly but is not incubated with test serum. These cells are used to determine the antibody titer of the indicator serum, as in the usual Middlebrook-Dubos technique[5].

All sera used are inactivated prior to use. Sera used as high titer "indicator sera" are absorbed on sheep cells and washed prior to use. Serial 1:1 dilutions of "indicator sera" are made with buffered saline and are incubated with O.T. sensitized cells for 3 hours at 37° C. They are left to stand overnight at room temperature and the degree of agglutination is read. (Overnight incubation may be omitted if cells are spun at 2,000 RPM for 1 minute.)

The following control measures were taken in every test:

(a) Two different "indicator sera" were used in each inhibition test.
(b) Hemagglutination titers were determined for each test serum and each "indicator serum."
(c) Heterophile antibody titer was checked with control tubes in each test and and a complete titration when indicated.
(d) The usual reagent controls were included in each run.**

Results. 1. The sera of hospitalized ill patients neutralized the O.T. antigen more than twice as often as did the sera of healthy control individuals. Marked or complete depression of the hemagglutination reaction was produced by the sera of 69% of the patients with sarcoid, by the sera of 75% of the tuberculous patients, by the sera of 74% of hospitalized ill patients with a variety of chronic diseases, but by the

*The 4 × O.T. used in these tests was obtained through the courtesy of the Lederle Laboratories.

**We are greatly indebted to Mrs. Jane Fenton of the Clinical Laboratory, Veterans Administration Hospital, for valuable technical assistance and suggestions.

sera of only 31% of normal healthy controls (Table 1).

2. Inhibition of the hemagglutination reaction was not specific, occurring about as frequently with the sera of patients with sarcoidosis, tuberculosis, or the miscellaneous group of diseases (Figs. 1, 2, 3, 4).

3. The ability of the patients' serum to neutralize the O.T. was independent of the source of high titer "indicator serum" used or the number of times tested. There were only two exceptions in the entire series where a serum depressed the reaction of one "indicator serum" and did not depress the others. Similarly if it did not depress the reaction of one "indicator serum," it did not affect the others. If it partially depressed one, it partially depressed the others. The serum of one patient with Boeck's sarcoid tested against 12 different "indicator sera" always completely inhibited the hemagglutination reaction.

4. There was no relation between the test patient's own hemagglutination titer and his inhibiting power as measured in this test.

5. There was no relationship between the patients' total serum proteins and the albumin-globulin ratio and the ability to inhibit the reaction.

6. Paper electrophoresis carried out on the sera of 6 normal controls, 3 of which inhibited and 3 of which did not, revealed essentially normal patterns in all cases.

7. Study of the amount of Forssman antibodies in 6 patients with varying abilities to inhibit revealed no relationship to the amount of Forssman antibodies.

8. Three of the 13 sarcoid patients had a positive hemagglutination test in dilution of 1:8 or higher. There was no apparent relationship between this titer in these patients and the ability of the serum to neutralize the O.T. antigen in the inhibition reaction.

9. The inhibiting effect of test sera evidently occurs through its action upon the O.T. or upon the sheep cell receptors. The net effect is the prevention of the O.T. from combining with or staying upon the sheep red cell. Introduction of the test serum after the sheep red cells were exposed to the O.T. produced no inhibiting effect.

TABLE 1.—EFFECT OF ADDITION OF VARIOUS TEST SERA UPON POSITIVE HEMAGGLUTINATION REACTIONS

Disease	*Total No. of Cases*	*Accentuation*	*No Inhibition*	*Slight Inhibition*	*Marked Inhibition*	*Complete Inhibition*	*Percentage with Marked or Complete Inhibition*
Sarcoidosis	13	1	3	0	3	6	69%
Tuberculosis	16	0	0	4	5	7	75%
*Chronically ill hospital patients	15	3	1	0	4	7	74%
Healthy Controls	74	8	18	25	13	10	31%

*See Fig. 4 for diagnoses.

Discussion. The tuberculin modifying factor, as we have found it, is no more common in sarcoidosis than in tuberculosis or in other diseases. However, it is found much less often in the sera of healthy controls. It is evidently not related to the "anergy" of sarcoidosis.

It seems likely that the tuberculin modifying factor we have found is the same factor noted by Wells and Wylie

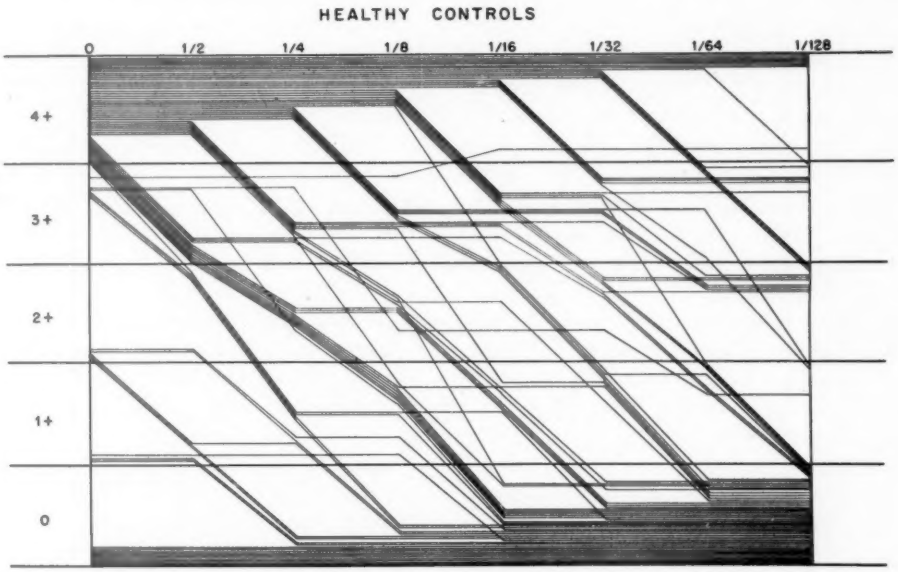

Fig. 1.—The inhibiting effect of test sera of healthy controls upon the positive hemagglutination reactions ("indicator sera"). The majority of reactions with "indicator sera" were not inhibited or depressed as shown by the 4+ reaction in the lower dilutions (1:1 to 1:16). An agglutination reading of zero indicates complete inhibition. Each line represents the complete titration for one test serum.

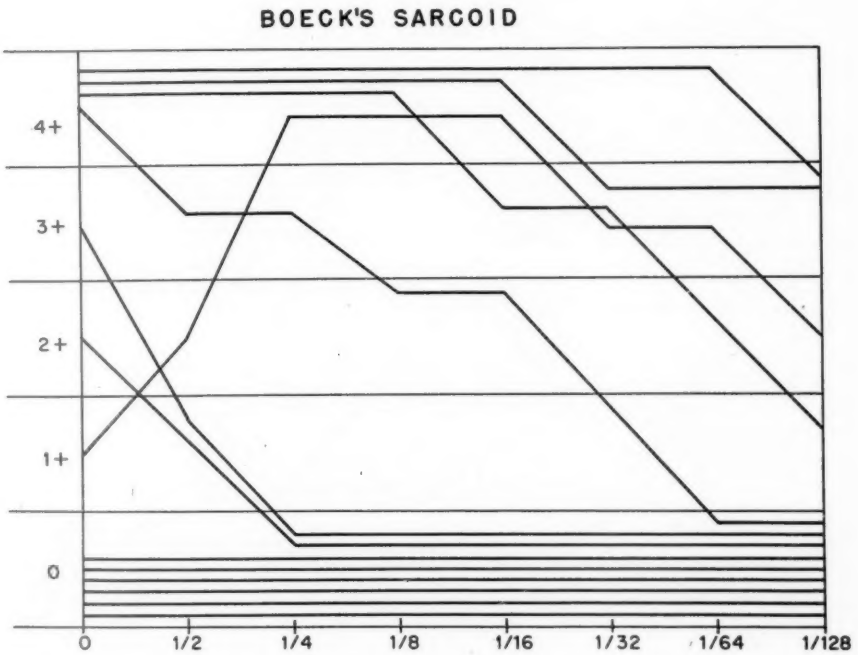

Fig. 2.—Inhibiting effect of test sera of 13 patients with sarcoidosis upon positive hemagglutination reactions ("indicator sera"). The majority (8) depressed the reaction with "indicator sera" in low dilutions, as evidenced by the absence of any agglutination.

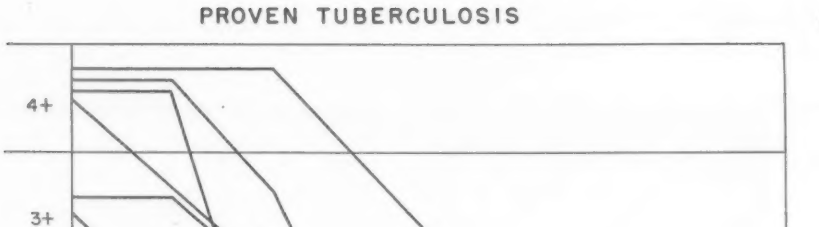

Fig. 3.—The inhibiting effect of test sera of 16 patients with tuberculosis upon positive hemagglutination reactions ("indicator sera"). The majority (12) depressed or inhibited the reaction in low dilutions.

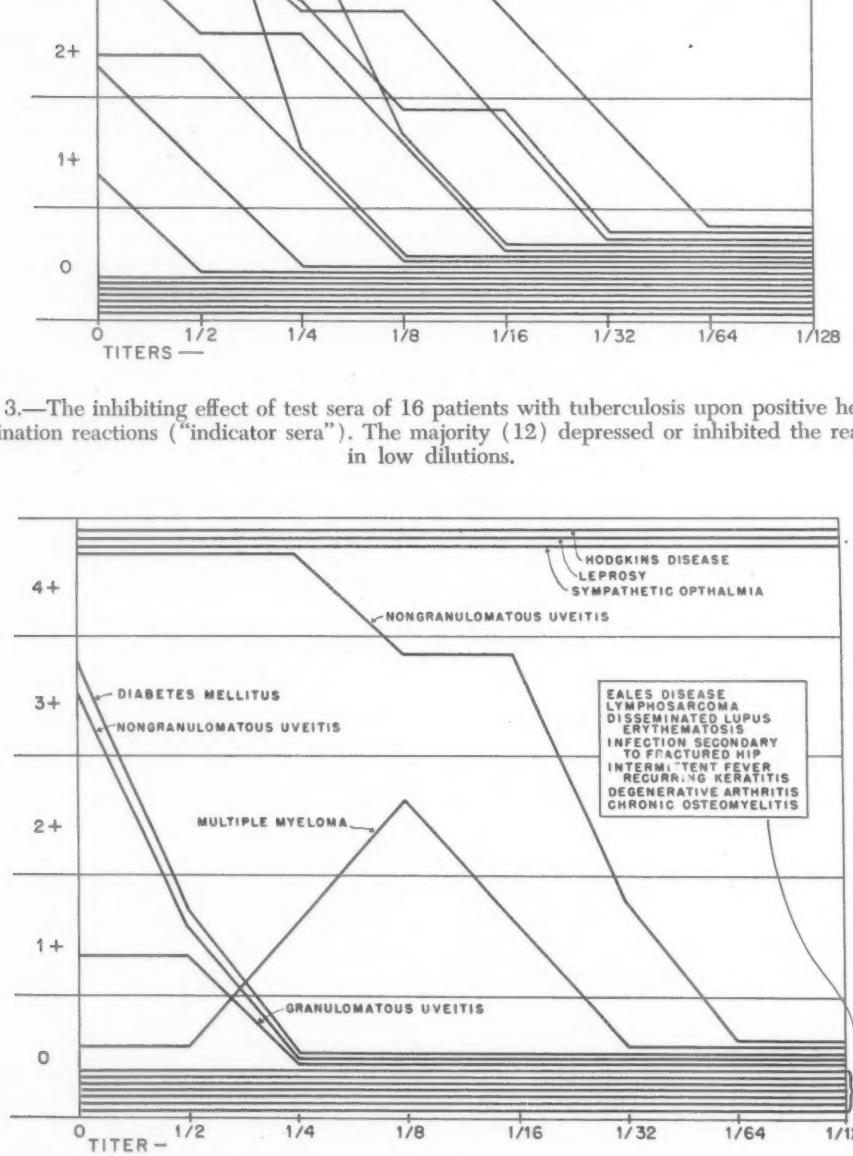

Fig. 4.—The inhibiting effect of test sera from patients with a variety of chronic diseases, ocular and systemic, upon "indicator sera." The majority exhibited a depressing effect upon the reactions with "indicator sera," as evidenced by the absence of agglutination in the lower dilutions.

in their study of the modifying effect of serum of patients with sarcoidosis on the tuberculin skin test. A small percentage of their control patients and patients with diseases other than sarcoid also exhibited the neutralizing effect. They did not look for the neutralizing factor in patients with tuberculosis.

The exact nature of this tuberculin neutralizing factor is unknown to us. Wells and Wylie, by electrophoretic separation, demonstrated in one case of sarcoid that their factor was a gamma globulin. Using paper electrophoresis, we found no difference in the patterns of normal patients who inhibited the reaction and those who did not. We noted no relationship between the total protein or albumin-globulin ratio of the serum and the ability to inhibit the reaction. Neter, Zolewski and Zak[4] showed that both lecithin and cholesterol strongly inhibit the hemagglutination reaction to *E. coli*. They demonstrated that the inhibitory effect is due to the action on the bacterial antigen rather than on the red blood cell, so as to interfere with the adsorption of the antigen by the erythrocytes. That the tuberculin modifying factor may be due to an increase in blood lipids is a possibility which we have not yet explored. The ability of the sera to prevent antigen from being adsorbed by sheep cells is not limited to the O.T. antigen. Working with *E. coli* hemagglutination reaction[2] we have found again that some sera will inhibit the reaction and others will not.

Conclusions. A nonspecific factor capable of preventing the adsorption of O.T. by sheep cells is sometimes present in human serum. It is found in approximately 70% of hospitalized ill patients and 30% of healthy persons. It is found no more often in patients with sarcoidosis than in other patients with a variety of chronic illnesses. The exact nature of the substance is unknown to us. At the present time it is of no value as a diagnostic test.

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RESULTS IN THE TREATMENT OF HUNTINGTON'S CHOREA WITH PROCAINE AMIDE HYDROCHLORIDE

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In 1952, Goldman[2] reported success in the treatment of Huntington's chorea with procaine amide hydrochloride (Pronestyl Hydrochloride).* In his series, 6 choreic patients were treated including 2 females and 3 males in a state hospital and one male patient seen in private practice. Clinical observations of improvement in the amount of choreiform movement were reported in all cases. The degree of improvement in the state hospital cases was described as ranging from "moderate" to "marked" while in the case of the patient seen in private practice, the choreic movements were described as "diminished almost to disappearance."

The very poor prognosis in Huntington's chorea together with the fact that there is evidence suggesting an increase in the incidence of the disease in the general population[4] points up the importance of careful evaluation of any new treatment which offers hope of success. As part of a larger investigation of the disease, we determined to evaluate the effectiveness of procaine amide in a selected group of patients with Huntington's chorea at the Rochester State Hospital.

Method. Three male patients were selected for study. Each had a positive family history of Huntington's chorea for at least three generations and had been hospitalized for at least 3 years. In addition, each was chosen because he appeared to have severe motor involvement without such severe intellectual or emotional impairment as would preclude cooperation with psychomotor test procedures.

Prior to beginning the medication motion pictures of the 3 subjects were taken during performance of a number of neurological examination procedures such as the finger to nose test, walking a straight line, and others in addition to normal daily activities such as lighting a cigarette. These pictures were intended to give a graphic record of the amount of choreiform movement.

Two standardized tests of motor dexterity were utilized. These were, the Seguin Form Board as presented in the revised Arthur Point Scale of Performance[1] and the O'Connor Finger Dexterity Test[3]. The former requires the subject to replace 10 blocks of different geometric shapes in the corresponding holes in a template using the preferred hand. The latter requires the subject to pick small metal pegs from a shallow dish and place them in holes of slightly larger diameter drilled in a brass plate. On both tests, the time in seconds constitutes the score. It was thought that the form board would reflect changes in gross eye-hand coordination while the peg board would give an adequate measure of any changes in coordination of fine finger movements.

The two tests were administered daily for a period of 10 days before medication was

*Pronestyl Hydrochloride is the brand name of procaine amide hydrochloride produced by E. R. Squibb & Sons, New York, who supplied the drug used in this investigation without charge.

instituted in order to establish a base line of performance for each subject. The purpose of the testing was explained to the subjects, two of whom cooperated with interest. The third patient who showed moderate intellectual deterioration cooperated for a time but later lost interest and refused to complete the test procedures.

Two patients had been selected in advance to receive the procaine amide medication. The third received as a placebo capsules of identical appearance containing calcium lactate as a control on the possibility that factors other than the medication might influence the choreiform movements under the experimental regimen.

Pronestyl Hydrochloride was administered for a period of 35 days as follows: an initial dose of four 0.25 gm. capsules; two capsules every 4 hours for 24 hours; and two capsules every 6 hours for the remainder of the period. It was thought that the 35-day test should be sufficient to reveal the nature and extent of any changes effected by the drug.

The patients were housed on the same ward of the hospital and observed daily. Throughout the time in which the medication was administered and for 30 days thereafter the two tests of motor dexterity were administered every other day, the recorded score on each day representing the average time in seconds for the best 10 out of a total of 15 trials.

Results. The two patients receiving the Pronestyl tolerated the dosage well and no untoward side effects were observed or reported by the subjects themselves. White count remained fairly constant throughout the study and no significant changes in blood pressure were noted.

Considerable variation was observed from day to day in the amount of choreiform movement in all 3 patients studied. There was, however, no consistent tendency toward improvement during the period of medication. In fact, performance on the dexterity tests indicated that the cooperative patient receiving Pronestyl and the control patient both tended to become slightly though not significantly worse during the course of the medication and after its cessation as compared with their baseline performance.

Motion pictures of all 3 patients taken after completion of the medication period failed to disclose any evidence of change in amount of choreiform activity when contrasted with the picture made earlier.

Discussion. Failure to vary the dosage up to the maximum which each patient could tolerate may have contributed to our negative results although it appears from the dosages reported in the previous study that this factor alone could not have been responsible for the disappointing response. The small number of subjects utilized also points up the fact that our study cannot be considered as a crucial test of the efficacy of the drug. We feel, however, that objective tests of motor dexterity as utilized in our study provide a highly desirable check on the reliability of clinical observation in assessment of changes in degree of involuntary motor activity in investigations of this type.

Summary. Two male patients with Huntington's chorea were treated with procaine amide hydrochloride (Pronestyl Hydrochloride, Squibb) while a third received a placebo. In contrast to findings in an earlier report, no improvement was noted in performance on objective tests of motor dexterity, in motion pictures before and after medication, or in clinical observation.

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PROGRESS
OF
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PEDIATRICS

UNDER THE CHARGE OF

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THE EVALUATION OF RENAL FUNCTION IN INFANCY AND CHILDHOOD*

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PRESENT day knowledge of renal function leads to the following concept of the kidney's operation: The hydrostatic pressure in the glomerular capillaries forces a volume of fluid into the glomerulus each day equal to approximately 10 to 15 times that of the extracellular fluid. By the combined processes of passive diffusion and active cellular transport, 99% of the filtrate with its dissolved salts is retrieved by the renal tubules. The tubular system may be thought of as constantly perfusing the extracellular space with an ideally composed fluid manufactured from a slightly less ideal glomerular filtrate[34]. What at first glance seems a wasteful and ill-conceived mechanism becomes, in this view, a process of high efficiency and one with enormous reserve against disease. Specific biochemical transfer systems exist for many of the substances salvaged by the tubule from glomerular filtrate. With such a concept of normal renal function, it could be predicted that clinical instances of disease involving specific biochemical tubular transport mechanisms should be found. Such indeed has been the case, and specific instances of disability of the tubule to exchange sodium for hydrogen ions, to reabsorb water, calcium, glucose, amino acids and phosphate have been found in recent years. While most instances of renal disease in children, as in

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TABLE 1.—A CLASSIFICATION OF DISORDERS OF RENAL FUNCTION AND INVESTIGATIVE PROCEDURES

Renal Function	*Blood Concentrations*	*"Routine" Procedures*	*Additional Studies*
Tubular Function:			
1. Maintenance of Body Fluid Osmolarity:			
Pseudo-diabetes insipidus[67, 75, 84, 100]	Na, Cl	Urine Sp. Gr., Conc. Dil. tests	Antidiuretic Response
2. Acidification of the Urine:			
Renal Tubular acidosis[3, 27, 43, 63, 70, 73, 105]	Na, Cl, CO_2, pH	Urine pH	Urine CO_2, Phosphate infusion
3. Regulation of Solute Concentrations:			
a) Sugar Renal Glycosuria[18]	Sugar	Urine Sugar	Chromatography
b) Amino Acids:[20, 36, 62, 130]			
Wilson's dis., Galactosemia, Cystinuria	Amino Acids		Urine A.A., Chromatography
c) Calcium: Idiopathic hypercalcuria[5]	Ca	Urine Sulkowitch	
d) Phosphate, under-reabsorption:			
D-Resistant Rickets[48, 82, 103]	Ca, P, Phosphatase		Response to Vit. D, Tm_{PO4}
e) Phosphate, over reabsorption:			
Pseudo-hypoparathyroidism[85]	Ca, P, Phosphatase		Parathormone Response, PO_4 clearance
f) Potassium: Brown *et al.*,[24] Earle *et al.*[46]	K	ECG	Potassium Balance
g) Unknown Organic Acids: Lowe *et al.*[74]			Urine Organic Acids
4. Combined defects:[16, 64, 74, 86, 87, 108]	Ca, P, Phosphatase	PSP excretion	Tm_{PAH}, Tm Glucose
Debre-de Toni-Fanconi, Lignac-Fanconi	Na, Cl, CO_2, pH		
Glycosuric Rickets	Sugar, Amino Acids		
Glomerular Function:			
1. Increased Permeability			
a) Protein: Nephrotic syndrome	Proteins	Urine protein	Quant. urine protein
b) Red Blood Cells: Acute Glomerulonephritis		Urine sediment Benzidine	Addis Count
2. Decreased Filtrations: Chronic Nephritis			Inulin Clearance
a) Urea, Creatinine	BUN, NPN Creatinine	Urea Clearance	Creatinine Clearance
b) Phosphorus, Potassium	P, K	ECG	

adults, result in symmetrical diminution of all components of renal function, a minority group of patients with highly specific losses of tubular function have been described. This concept of renal disease as a single or combination of single functional disorders has been emphasized by Jackson and Linder[64], Fanconi[47] and by Myerson and Pastor[87]. It is the purpose of this review to describe the clinically applicable methods for documenting such specific defects as well as methods for evaluation of over-all renal function in children.

Table 1 presents a classification of renal disease in terms of specific functions and the examinations which are useful in studying these functions clinically. When considering this method of classification, a number of points must be kept in mind: a) Each defect may occur singly or in combination with others. b) Although most of the reported defects have been congenital in origin, a few seem to have been acquired. c) Such defects initially may be predominantly tubular, yet, as the renal disease progresses, glomerular insufficiency may dominate the findings. d) Generalized kidney disease with relatively equal disturbance in each of the facets of renal function is most common and is apparent in many of the individual functional studies and in the broader screening ones as well.

Because of wide variation in size, some basis of comparison among children themselves and between children and adults is needed. This problem has been reviewed by others, and weight, height, kidney weight, body water, basal metabolic rate and surface area have been suggested as standards of reference[101,109]. At present, the most commonly used reference is the "ideal" adult surface area of 1.73 m^2. Once a basis for comparison has been established, the change in these functions with growth must be ascertained. Maturation of renal function with growth has been reviewed by McCance[77,78], Smith[109] and Barnett[7]. Some of the previous work, as well as that done since the above reviews, will be covered in this discussion. Of necessity, investigations that do not have clinical application at this time have not been included.

I. **Indirect Clinical and Laboratory Studies.** Before discussing studies involving analysis of the urine, other methods of investigation should be mentioned, for often the clues leading to the indictment of the kidney, as well as much of the evidence of its culpability, may be obtained in these indirect ways. Two nonspecific findings, which may be obtained in the history or on physical examination and may point to the kidney, are retardation in growth and fever of unknown origin: The fever may be from renal infection or on the basis of dehydration resulting from an obligatory polyuria. Specific urinary symptoms which are occasionally dismissed without investigation or are not specifically sought for are polyuria, the size and force of the urinary stream in males and the distinction between enuresis and incontinence. If these symptoms and signs are looked for routinely, many of the cases of obstructive uropathy can be diagnosed before severe damage has occurred[88]. Obviously on physical examination such things as unexplained dehydration, edema, hypertension, hyperventilation, costovertebral angle tenderness or abdominal masses lead one to consider a possible renal lesion.

Examination of the blood as a representative of the body fluids frequently incriminates the kidney. Anemia is characteristic of chronic renal disease and may be the presenting problem in such cases. Elevation of blood urea nitrogen, nonprotein nitro-

gen or creatinine immediately focuses attention on the kidney, but normal values certainly do not rule out many serious renal disturbances. If other explanations are not obvious, sudden or persistent acidosis, abnormalities of sodium, potassium, chloride, calcium or phosphorus concentrations, elevation of alkaline phosphatase, or decreased serum protein concentrations may well be significant indications to investigate renal function.

Renal disease may be suggested by rickets, osteomalacia, or osteoporosis as well as by roentgenographic examination of the urinary system. In the roentgenographic examination of the urinary tract, the plain film (KUB) may be studied for abnormality of size, shape and position of the kidney and the presence of abnormal renal densities. Excretory pyelography should be carried out in all suspected cases of renal disease except in the presence of severe renal failure. The excretion of the dye is by both glomeruli and tubules; the protein-bound fraction is excreted by the tubules and the free dye by the glomeruli. The study, therefore, is not only valuable as a means of visualization of the structure of the excretory system, but the concentration of the dye as seen on the film is a measure of over-all renal function. Pre-test preparation of the infant's gastrointestinal tract by cathartics or enemas, or both, is of little value in improving the radiologic appearance of the abdomen and should not be done. A better method of improving the results in infants is to double the amount of dye that is given[28]. If intravenous administration of the dye is technically difficult, some of the dyes (for example Diodrast) may be given intramuscularly, with half the calculated amount in each gluteal area; or subcutaneously after diluting 1:5 with 0.9% sodium chloirde.

Failing to obtain satisfactory studies by excretory pyelography, the next logical roentgenographic procedure should be cystography. This should be done immediately after a spontaneous voiding in order to measure the residual urine as well as to inject the radiopaque material into the bladder. With cystography, an extremely valuable finding which should always be sought is retrograde filling of the ureters. If present, this is an abnormal finding. On this examination, study of the urethra during voiding of the radiopaque material also may be done[50]. Failing to elucidate the etiology of a renal lesion by these means, retrograde pyelography should be performed.

II. **Specific Tests of Renal Functions.** Reference to Table 1 clearly indicates that a "routine" urinalysis properly performed will provide information on most of the discrete functions to be studied.

The collection of urine for study may prove the most difficult part of the investigation, particularly in girls.

One of the most common methods in current use for collecting a single specimen from untrained female infants is the use of a birdseed cup strapped in place until the child has voided. The chief objections to this method are that the amount of urine obtained is small and it is frequently contaminated with stool and debris from the perineal region. In the female infant there is no satisfactory substitute except catheterization or the more elaborate apparatus described by Black[17]. In boys ordinary test tubes can be used, and satisfactory glass adapters have been described[17]. With small (No. 10 Fr.) firm rubber, retention catheters, collections are quite satisfactory. Catheter collections are essential if precisely timed specimens are required.

A. TUBULAR FUNCTIONS. *1. Concen-*

tration and Dilution of Urine. The ability of the kidney to vary the excretion of water in relation to solute is the primary means of maintaining body fluid osmolarity. In other terms this involves the ability of the kidney to concentrate and dilute urine or to respond to diuretic and antidiuretic stimuli. Inability to concentrate or dilute urine is one of the central features of chronic generalized renal disease; the maximum concentration and dilution range which can be achieved narrows as the disease progresses and eventually the urine concentration becomes the same as that of a glomerular filtrate with a specific gravity of 1.010 and a solute concentration of about 300 milliosmols per liter. In contrast to this, cases of diabetes insipidus, pseudodiabetes insipidus[75], and "water losing" nephritis[100] produce a urine that is very dilute (1.001 to 1.003 Sp. Gr., 50 to 100 m-osM./L.) and only under marked dehydration are able to raise the concentration of their urine to the level of a glomerular filtrate or slightly above it.

The specific gravity of a random urine often is all that is necessary to eliminate many problems. A specific gravity greater than 1.025 in a dehydrated child rules out most cases of generalized renal failure as well as the diabetes insipidus-like states. Specific gravities of less than 1.005 with normal hydration raise the possibility of a water-losing syndrome. The specific gravity in the well-hydrated child is usually between 1.005 and 1.025. Frequently the volume of urine available is too small to measure specific gravity in the usual urinometer. Micro methods utilizing comparison with nonmiscible solutions of varying density are available[21,41,65]. Vapor pressure, surface tension and refractometry have also been used to measure the amount of total solute in the urine, but are not clinically applicable. Freezing point depression as a method of measuring osmolarity is widely used and has the advantage of requiring only 1 to 2 cc. of urine. The actual measurement of the colligative properties of the urine reflects renal function more accurately than the specific gravity, since urines with the same specific gravity may have somewhat different osmolarity and *vice versa*[96]. The theoretical disadvantages of the cryoscopic technique are the changes in osmotic activity and solubility between 37° C. at which the urine is formed and 0° C. at which the osmolarity is measured.*

Concentration tests are performed when single specimens do not give definitive results. Thirsting for 6 to 24 hours, depending on the tolerance of the patient, is sufficient to promote good concentration in children (Sp. Gr. greater than 1.025). Undiluted evaporated milk formulas may be given to infants and produce near-maximal urine concentrations in 24 to 48 hours[95]. This method avoids the necessity of starving infants in order to thirst them.

In patients with diabetes insipidus or similar disorders, a 6-hour period of thirsting is often all that is required as the patient is quite dehydrated, febrile and appears ill by this time. The urinary concentration does not exceed 1.015 and is usually less than

*Specific gravity, solute concentration, and "water concentration" correspond roughly as follows:

1.001	50–100 m-osM./Liter	20–10 cc./m-osM.
1.010	300–350 " " "	3.0 " " "
1.020	600–700 " " "	1.5 " " "
1.030	1000–1200 " " "	1.0–0.8 " " "
1.040	1400–1600 " " "	0.7–0.6 " " "

1.010. Urine flow calculated as cc./min. is also helpful but may show considerable reduction even in diabetes inspidus. In children a weight loss exceeding 1.0 kg./meter^2 (4% of the body weight) in 6 hours' dehydration is considered to signify a loss of the normal water conservation mechanism[119].

This capacity to maintain weight when thirsting is apparently just as adequate at birth as in the adult. Newborns thirsted for the first 3 days of life had an average weight loss of 2.0 kg./m^2/day compared to 2.4 kg./m^2/day for adults. This appears to be true in spite of the fact that the urinary concentration at the end of the 3-day thirst was 650 m-osM./L. in the infant and 1400 m-osM./L. in the adult[56]. That the concentrating power of the infant's kidney is diminished, is also discussed by Heller[58]. However, some infants can apparently concentrate further as shown by Thomson[121] who found a specific gravity of 1.030 in a newborn infant with dehydration fever. Barta and Hernandi[13] also concluded that the "tubular reabsorption of water is already perfect in the earliest period of life." This ability to concentrate urine is not well maintained when the dehydration is due to illness instead of the result of simple lack of fluids[30,45]. Calcagno[29] has shown that premature infants have a lesser capacity for water conservation than do normal adults.

Measurement of hematocrit, BUN and serum sodium or chloride concentrations are valuable adjuncts to the concentration test but are not essential.

The reverse procedure, that is, dilution tests or water loading, can be carried out quite easily as a clinical study and provide worthwhile data if performed in a standard way. Commonly this is done after a moderate period of fluid restriction (6 to 12 hrs.). An oral water load equivalent to 3 to 5% of the body weight (30 to 50 cc./kg.) given in a 30-minute period is usually well tolerated. It may be given by stomach tube in infants. Urine collections are best made at 15-minute intervals beginning prior to the administration of the water. A peak of the diuresis should occur at from 50 to 120 minutes following completion of the water ingestion. The intensity of the diuresis is variable depending upon the prior state of hydration of the infant. When the urine flow is corrected for surface area, the peak flow is 10 to 20 cc./min./1.73m^2 in older children and adults[134], and in the newborn is about half of this value[11,80]. When water loading was done on normal infants in the first day of life, no diuretic response was obtained by Ames[6]. By 7 days of age, she noted that 50% of the administered water was excreted in 3 hours; and after 2 weeks of age, 100% of the water was excreted. There was no difference between premature and full-term infants. Barnett and associates[11] noted that by 36 days of age, premature infants were showing the same diuretic response as adults when compared on a surface area basis, but the peak of urine flow occurred 20 to 30 minutes earlier than in the adult. McCance[80] has shown that correction of the flow to a total body water basis makes the newborn's diuretic response quite similar to the adult's except that again the peak of the diuresis tends to occur earlier in the infant.

Changes in the concentration of serum constituents would be quite enlightening during water loading. However obtaining the necessary blood samples is not feasible, as an antidiuresis is produced too often[68,102].

Intravenous infusion of 5% glucose provides a good baseline upon which to evaluate various antidiuretic stimuli. After a moderate period of fluid restriction, an infusion of 5% glucose

equivalent to 20 cc./kg. is given at a constant rate for one hour. The rate is then changed to 15 cc./kg./hr. for 45 minutes. The urine collections are again made at 15-minute intervals and carried on for 60 minutes following the conclusion of the infusion. The peak of the diuresis is from 60 to 90 minutes after the start of the infusion and is lower than on the larger oral dose.

Individuals with chronic renal insufficiency show very little response to these water loads. As a rule, there is no sharp peak and the response is prolonged[134]. Similar responses are reported in individuals with primary defects in the mechanism for facultative water reabsorption, for example, diabetes insipidus, pseudo-diabetes insipidus[49,134]. However, if the individual is quite dehydrated when the test is performed, the response may be deceptively like that of the normal.

Hypothalamic receptors exist that are sensitive to changes in plasma osmolarity; these receptors reflexly control the rate of antidiuretic hormone (ADH) production by the posterior pituitary[127]. In turn, ADH controls the tubular reabsorption of water[71]. It is possible to examine this sequence at each level.

If an antidiuresis follows the infusion of hypertonic saline, the entire system is intact[31,60]. A high rate of urine flow is established by the infusion of 5% glucose as described above. After 60 minutes, a 2.5% solution of sodium chloride is substituted for the glucose, and the infusion rate is changed to 15 cc./kg./hr. or 0.25 cc./kg./min. for 45 minutes. The response curve can be compared with that resulting from the glucose alone.

Dehydrated individuals[39] and patients who are unable to concentrate their urine[67] often show a diuretic response to hypertonic saline rather than an antidiuretic one. Failure to exhibit antidiuresis in response to hypertonic saline is usually followed by measuring the response to aqueous pitressin. Talbot[118] recommends the intravenous or subcutaneous administration of two units/m^2. As indicated by Talbot[119] and White[134], the first time that pitressin is given in true diabetes insipidus, the response is not great but improves with subsequent administration. For the pitressin test the glucose solution is started as noted above, the pitressin being given 60 minutes after the fluids have been started. The response is again compared with that of the glucose given alone. This may be more precisely quantitated by calculating the "per cent inhibition" as described by White *et al.*[135] or the "free water clearance" as discussed by Wesson and Anslow[131].*

As with water diuresis, antidiuresis is progressively improved with increasing maturity of the infant. In infants under 3 days of age, Ames[6] found no antidiuretic effect although antidiuretic activity was found in the urine of these children. By 5 days of age the response was like that of the adult but was of shorter duration. Heller[58] also found the renal tubules of the infant less responsive than the adult's to antidiuretic hormone. Patients with chronic renal insufficiency[134] and with pseudo-diabetes-like states also show diminished or absent antidiuretic response to pitressin[67,75,100].

An intermediate step in the investigation of these problems is the use of nicotine to produce an antidiuresis. It

$$\text{*Per cent inhibition} = \frac{\text{Expected diuresis} - \text{Observed diuresis}}{\text{Expected diuresis}} \times 100$$

$$\text{Free Water Clearance } C_{H_2O} = \left(1 - \frac{\text{Uosm}}{\text{Posm}}\right)V$$

Uosm = Urine osmolarity
Posm = Plasma osmolarity
V = Urine flow (cc./min.)

is postulated that if the osmoreceptor, and not the posterior pituitary, is diseased, there will be a response to nicotine and pitressin and not to hypertonic saline[41]. The dose of nicotine that has been used in some experimental studies is 1 to 4 mg.[72]. Cates and Garrod[32] obtained a response to large doses of nicotine which was of the same order of magnitude as the response to hypertonic saline in the patients with diabetes insipidus.

2. *Acidification of Urine.* Children on the usual American diet excrete an acid urine[107]. During dehydration, fasting, diarrhea, and the like, the urine is normally quite acid in an attempt to conserve fixed cations.

The most commonly accepted mechanisms by which this is accomplished in man have been reviewed recently by Gilman[52]. First, hydrogen ions are exchanged for sodium or other fixed cations. The extent to which this can be done is limited by the hydrogen ion (H) concentration in the urine (pH). However, the more H^+ in the urine, both ionized as well as unionized, the greater is the titratable acidity. This is determined by titrating the urine to pH 7.4 with a standard alkali[93]. Albright[4] recommends the addition of a known amount of hydrochloric acid prior to alkali titration. Much of the exchange of H^+ and Na^+ in the urine occurs with buffer salts like Na_2HPO_4 which is converted to NaH_2PO_4 by the exchange mechanism.

The second mechanism for removal of acid is the production of ammonia. In an acid urine the ammonia (NH_3) which diffuses freely, combines with ionized hydrogen (H^+) to form NH_4^+. The net effect is to raise pH, that is, decrease H^+ concentration without changing the titratable acid, or total hydrogen ion present. In general the two mechanisms go together, but it is reported in some cases of Fanconi's syndrome that there is increased ammonia formation in relation to the titratable acid[64]. The reverse situation has not been reported yet.

The measurement of the pH of the urine is of aid in evaluating the kidney's acid-base regulating ability. The pH of the urine should be measured on a freshly voided specimen and done either with a pH-paper which will distinguish differences of half a pH unit, (for example, nitrazine) or with a pH-meter. A urine of pH 5.5 or lower usually indicates good renal function in terms of ability to produce an acid urine. This pH is not usually attained unless the child is acidotic as a result of diarrhea, dehydration, and the like. The reverse situation of an alkaline urine in alkalosis does not necessarily occur[126]. Children with hyperchloremic acidosis (renal tubular acidosis) do not make an acid urine even when the blood pH is reduced[3,27,43,63,70,73,109].

When there is question concerning this function, several provocative tests have been suggested. The administration of ammonium chloride has been used to produce mild metabolic acidosis in a normal individual. However, in severe renal diseases an irreversible acidosis has resulted[26]. Because of this danger, safer methods should be sought. One such procedure is the administration of an isotonic buffered solution of $Na_2HPO_4 : NaH_2PO_4$ in a ratio of 4 : 1[70]. (A study that can be done concomitantly is the measurement of phosphate clearance and Tm.) Latner and Burnard[70] administered 5 to 8 gm. of ammonium chloride in the 18 hours prior to the phosphate infusion to provide a need for base conservation. Caution in the administration of ammonium chloride is again advised. In patients with a renal type of acidosis requiring alkali supplementation to maintain a normal serum pH, adequate acidosis can be produced by

discontinuing medication for 24 hours. In normal children, Latner and Burnard[70] obtained values for titratable acidity of about 50 μEq./min./1.73m^2 before the phosphate infusion and 500 μEq./min./1.73m^2 following it.

In their series of patients with hyperchloremic acidosis, the titratable acidity was considerably less than 50 μEq./min./1.73m^2 before the phosphate infusion, and the urinary bicarbonate was elevated; after phosphate, the titratable acidity rose and the bicarbonate excretion was decreased. It is not known whether all patients with hyperchloremic acidosis respond similarly.

The ability of very young, normal infants to respond to such an infusion compared with older children and adults has not been ascertained. Gordon *et al.*[54] gave ammonium chloride (4.8 gm./m^2) to premature and full-term infants and observed a greater increase in titratable acidity and ammonia production in the full-term babies. Experiments by Cort and McCance[35] indicate that puppies respond less adequately to an acid load than do older dogs, but the puppy's response improves rapidly with age. McCance and Finck[79] have shown that even on the first day of life, a random urine specimen from a newborn child has about the same amount of titratable acid as an adult's. The titratable acidity in the urine of an average adult is about 25 μEq./min.[125] and was found by Pitts[94] to increase to about 35 μEq./min. after 20 gm. of ammonium chloride and to increase tenfold after an infusion of buffered phosphate.

3. Regulation of Certain Specific Solutes. a) SUGAR. Examination of the urine for reducing substance by the use of Benedict's solution is not only of value as a diagnostic procedure in diabetes mellitus, lead poisoning, brain tumors, galactosemia, and others, but glucosuria has also been noted to occur as a single renal defect in renal glycosuria and as a feature of the more complex Fanconi-type syndromes. A scheme for differentiating the various reducing substances in urine is given in Table 2 which is modified from Ham[55]. Quantitation of urinary sugar is readily accomplished by the use of the Somogyi reaction[113], and a comparator is commercially available.* More elaborate study of urinary sugars can be carried out by paper[15,59,66] and column[61,133] chromatography.

b) AMINO ACIDS. Amino acid excretion is of considerable interest at present. The determination of urinary amino acids is usually a research procedure although both chromatographic[15,40,59,115] and alpha-amino N analyses[2,14,40,92] are being used more widely. Abnormal excretion has been noted in galactosemia, Wilson's disease, uranium poisoning and the Fanconi syndrome (see Table 1). Normal values for children depend on the method being used[33,89,116].

c) CALCIUM. An additional study which can be done routinely and will give some information from a single urine specimen is the Sulkowitch test for calcium[12,120]. In doing this procedure, as in all screening tests, the limitations of the method must be kept clearly in mind. Two important considerations in the Sulkowitch test are the calcium intake of the individual, especially in children, and the concentration of the urine. An abnormal amount of calcium is present in the urine in idiopathic hypercalcuria[5] and overdosage of vitamin D; no calcium is found in the urine in tetany due to hypocalcemia.

Use of testing procedures for ace-

*Somogyi Urine Sugar Comparator. A. S. Aloe Company, St. Louis, Missouri.

tone bodies does not constitute a test of renal function but is mentioned because it is a part of a routine urinalysis. The use of 10% ferric chloride not only reveals the presence of acetoacetic acid but also is positive in the presence of salicylates. It remains positive after boiling when the color is due to salicylates but is negative after boiling if the color is due to diacetic acid. A very dark green color results when phenylalanine is present. The procedure is therefore diagnostic in the recognition of phenylpyruvic oligiphrenia[55].

TABLE 2.—IDENTIFICATION OF URINARY SUGARS

Sugar	*Test*				
	Reduction of Benedict's Solution				
	At 100° C. for 5 min.	*At 55° C. for 10 min.*	*After Yeast Fermentation*	*Seliwanoff Reaction*	*Orcinol Reaction*
Pentoses	+	+	+	0	+
Fructose	+	+	0	+	0
Glucose (>4%)	+	+	0	0	0
Glucose (<4%)	+	0	0	0	0
Maltose	+	0	0	0	0
Lactose	+	0	+	0	0
Galactose	+	0	+	0	0
Non-carbohydrates	+	0	+	0	0

(Modified from Ham, T. H. [55])

TABLE 3.—QUALITATIVE ESTIMATION OF URINARY PROTEIN

Amount of ppc.	*Scale*	*Approx. Prot. Conc. (mg. per 100 cc.)*
None	0	0
Slightly Turbid	Trace	1 to 10
Turbid (can read print through it)	1+	15 to 30
Cloud—no ppc. (can see heavy line through it)	2+	40 to 100
Cloud—fine ppc. (cannot see heavy line through it)	3+	150 to 350
Flocculent ppc. to solidification	4+	600 to 2000

(Modified from Ham, T. H. [55])

B. GLOMERULAR FUNCTION. *1. Increased Permeability.* The routine determination of urinary protein is best carried out by heating and acidifying the urine after the urinary sediment has been centrifuged. Table 3 shows the relation between the amount of precipitate and the actual protein content by this method[55]. A slightly more quantitative test is done with the use of 3% sulfosalicylic acid and comparing with standard solutions[69]. The method of Shevky and Stafford[106] is the most quantitative procedure for general clinical use.

The microscopic examination of the urine sediment should always be done on a fresh specimen which is centrifuged and the sediment resuspended in a few drops of urine. Careful scrutiny of the sediment discloses a great deal of a qualitative nature about the patient's urinary tract; experience is most valuable in this regard. There is a poor correlation between the number of cells and casts seen on the routine examination of urinary sediment and on the more quantitative Addis count; this is especially true for red cells[76]. If only an occasional white cell/HPF is seen, this is usually normal. The absence of erythrocytes and casts on a routine urine does not preclude an abnormal number on an Addis count; similarly, the presence of occasional to

1 to 2 RBC/HPF does not always signify an abnormality. The presence of more than 1 to 2 cells/HPF is almost always abnormal and in most acute situations, the number of cells seen on the routine examination is adequate to establish a diagnosis.

A more quantitative approach to the determination of pyuria on the basis of examination of a single specimen has been made by Stansfeld and Webb[114]. They suggest counting the cells of an uncentrifuged urine in a regular counting chamber; they found 98% of the male children had less than 10 cells/mm^3. This was also true of catheterized specimens in girls, but with noncatheterized urines, only 84% had less than 10 cells/mm^3. When the qualitative examination of the urinary sediment is not obviously abnormal, a more quantitative estimate is accomplished with an Addis count done on an overnight, 12-hour collection. The specific gravity of the urine should be over 1.020 for the best results; if it is below 1.010, the red cells hemolyze and the hyaline casts dissolve too rapidly. The Addis count figures for normal children are given in Table 4.

TABLE 4.—ADDIS COUNT IN NORMAL CHILDREN

(12-hour specimen, 312 children[51,76,97,112])

	Casts	*R.B.C.*	*W.B.C.*	*Protein (mg.)*
Range	0 to 29,000	0 to 800,000	9,000 to 2,800,000	3 to 90
Average	1,200	50,000	320,000	24
Suggested upper limits of normal	10,000	600,000	2,000,000	55

2. CLEARANCE TECHNIQUES. The clearance of a substance equals the amount of plasma or ultrafiltrate which would provide the quantity of the substance appearing in the urine, per unit time. The first requirement in calculating a clearance is to know the amount of the substance which is filtered through the kidney. For a substance which is only filtered, the amount excreted is a measure of the amount of glomerular filtrate being produced.

Example:

Plasma concentration (P) = 15 mg./100 cc. = .15 mg./cc.

Urine volume (V) = 20 cc. in 10 minutes = 2 cc./min.

Urine concentration (U) = 300 mg./100 cc. = 3.0 mg./cc.

Thus in one minute the excretion would be 6 mg. (there are 2 cc. being excreted per minute and each cc. contains 3 mg. $V \times U = 6$). Then it would take $\frac{6}{.15}$ or 40 cc. of plasma to provide the 6 mg. in one minute. Therefore, the clearance (C) = 40 cc./min.

The general formula is expressed

$$C = \frac{UV}{P}$$

For any substance, the amount filtered can be calculated by multiplying the glomerular filtration rate, (for example, the clearance of inulin) by the concentration in the plasma of the material being studied. The difference between the amount in the urine and the amount which has been filtered through the glomerulus is the fraction which has back-diffused, been reabsorbed or been secreted by the tubules. These functions can be measured for a variety of substances as shown in Table 5. The major problem with those substances that are acted on in the tubules is that glomerular filtration rate must be measured simultaneously in order to evaluate tubular function. The length of the individual collection periods that should be used to meas-

ure clearances depends on several factors: a) the time necessary to measure urine flow accurately; b) the possibility of variation in the clearance with changing urine flow (for example, urea); c) constancy of the blood level; and d) the physiological significance of the time interval used. It should be borne in mind that any clearance may vary from day to day and hour to hour. A single clearance period, therefore, is unreliable, and at least two or three periods are necessary to approximate the actual clearance of a material.

TABLE 5.—MECHANISMS OF EXCRETION

A *Glomerular Filtration only*	*B* *Filtration and Back Diffusion*	*C* *Filtration and Active Reabsorption*	*D* *Filtration and Active Secretion*
Inulin Mannitol	Urea	Glucose Phosphate Amino Acids Na, Cl.	PAH Diodrast Phenol Red
Other Endogenous Creatinine (*A*) or (*B*) Potassium (*C*) and (*D*) Thiosulfate (*C*) and (*D*)			

Urea clearance has long been used as a measure of renal function[91]. Rubin[101] has shown that it may reflect glomerular filtration rate in children by assuming a constant fraction (40%) of filtered urea is reabsorbed. It is generally accepted that a larger proportion of the urea is reabsorbed at low urine flows, that is, below the augmentation limit, and that there is also considerable individual variaton at urine flows above the augmentation limit of 2 cc./min./1.73m^2 [91]. Furthermore, Barnett *et al.*[9] and McCance and Young[81] found that urea clearance in infants continued to increase at urine flows above 2 cc./min./1.73m^2, but Gordon *et al.*[53] could not demonstrate this. Recently, Bruck[25] has made a study of simultaneous urea and mannitol clearances in sick and in healthy children and concludes that glomerular filtration rate will not be less than the urea clearance nor more than four or five times greater than urea clearance. The tendency to diminishd reabsorption of urea was more marked in patients with diseased kidneys than in normals and was not seen when the mannitol U/P ratio was greater than 100. Only one normal infant had excessively high urea reabsorption, but this did occur occasionally in patients with nephrosis. The exact relation of urea clearance to filtration rate is thus in question and, as Bruck points out, further work using simultaneous inulin and urea clearances is indicated. Because of the ease with which urea clearances can be done and their widespread clinical usage, they remain a useful test of over-all renal function. Serial determinations are valuable in following the course of a patient with chronic renal disease.

A second procedure utilizing a naturally occurring substance is the endogenous creatinine clearance. The principal problem with this technique is in methodology. The analysis of total creatinine chromogens includes true creatinine plus the noncreatinine chromogens in a ratio of 3 to 4:1 in normal individuals[22,57]; the clearance of the noncreatinine material is less than for true creatinine[1,22]. Depending on the method used, creatinine clearance

may be equal to glomerular filtration rate[1,19,57] or less than it is in children[23,44]. In children with diseased kidneys, the relation of creatinine to inulin clearances is also inconstant. The chief advantages of the endogenous creatinine method are that there is very little change with urine flow and serum creatinine is not affected by protein intake. This allows prolonged clearance periods, but diurnal variations do occur and should be considered in 24-hour clearance periods[1]. Variations also result from changes in the emotional state of the individual[104].

The clearance and maximal tubular reabsorption of phosphate and P^{32} have been investigated[38,83,98,117]. The relative inability of the infant kidney to excrete phosphate is a factor in the genesis of newborn tetany. The data on phosphate clearance are included in Table 6.

The clearance of other endogenous substances may be calculated in the same way, but the clinical significance of most of these measurements in children is still unknown.

Clearances of exogenous materials are calculated similarly. The major difference is that the exogenous substances must be injected and the fluids thus administered may alter the function being studied. In the usual procedure the infusion is at a constant rate to assure a steady blood level during the collection periods. Several investigators have done these studies using a subcutaneous injection with or without hyaluronidase to measure glomerular filtration rate (GFR) and effective renal plasma flow (ERPF)

TABLE 6.—AVERAGE VALUES FOR CLEARANCES IN CHILDREN

Age	*Premature*	*Newborn*	*3 mos.*	*6 mos.*	*12 mos.*	*18 mos.*	*24 mos.*	*Adult**
Clearance	(cc./min./1.73m²)							
Urea	25	30	45	50	60	70	70	70
Endog. Creatinine				75	100			100
Mannitol	45	50	70	105	120	125	125	125
Inulin	45	40	70					125
Diodrast		70						650
PAH	150	200	300	500	550	600	650	650
Phosphate		7		13			15	17
Tm	(mg./min./1.73m²)							
PAH	13	25	40	65	70	75	75	75
Glucose		60	170					350
REFERENCES								
Urea	12, 10, 136	12, 37, 81, 101, 122, 136	10, 12, 81, 101, 137	81, 101, 137	101	101	101	
Endog. Creat.				44	44		44	
Mannitol	10	101, 132	10, 101, 132	101, 132	101, 132	101,132	101, 132	
Inulin	10	37,81, 129	10, 124, 129					
Diodrast		37						
PAH	10	101, 129, 132	10, 101, 129, 132	101, 132	101, 132	101, 132	101, 132	
Phosphate		38, 83, 98		38			98	
Tm PAH	10	101, 132	10, 101, 124, 132	101, 132	101, 132	101, 132	101, 132	
Tm Glucose		123	124					

* Approximate figures; both sexes combined

and have obtained quite satisfactory results[44,128]. This would seem to be a useful method for many clinical investigations.

Barnett[8] has suggested the use of a single intravenous injection to measure the glomerular filtration rate in infants by measuring the slope of the falling blood level and thus avoiding the neccessity of collecting urines. The standardization of this procedure has not been published and it is not in wide use at this time. A common clinical modification of this technique is the single injection of phenol red (PSP). The dye is excreted by renal tubules; at low concentrations in normal individuals it is almost completely removed from the blood as it flows through the kidney. Thus the clearance of PSP, as well as of PAH and Diodrast at low concentrations is a measure of the effective renal plasma flow (ERPF). At high concentrations these substances can be used to measure the maximal capacity of the tubules to excrete them (Tm)[109]. With phenol red, however, the modification that is in common clinical use is that a single injection of the material is given intravenously and the per cent excreted in various time intervals is measured. In this rough form the test is not too valuable a measure of tubular function or of renal plasma flow, but the excretion in the first 15 minutes, normally at least 25% of the dye, does give useful information about kidney function in general; and as with urea clearance, serial studies aid in the evaluation of chronic kidney disease. No standards are available for infants.

For specific measurements, the presently accepted clearance materials are inulin for glomerular filtration rate, low concentrations of para-aminohippurate for effective renal plasma flow, high concentrations of PAH for maximal tubular excretion, and glucose for maximal tubular reabsorption. The techniques for these determinations are well described and are clinically practical[99,110,111]. It is well to remember that sulfonamides interfere with PAH analyses.

In children under 2 years of age the normal values for glomerular and tubular functions are considerably reduced when calculated on the basis of surface area. These values are lowest in the premature infant and increase with age; they tend to be in the normal adult range by the time a child reaches 2 to 3 years of age. Tubular functions appear to be more depressed than glomerular and approach the adult levels more slowly[90,101]. The average values at several ages are given in Table 6. There is an extremly wide range of normal values at every age, and at present this normal range is not well defined. The spread of values is greatest in the newborn and may reflect differences in age, weight, or urine flow.

Summary. The diagnosis of specific and generalized disturbances of renal function in children has been considered, utilizing clinical, roentgenologic and laboratory examinatons.

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GYNECOLOGY AND OBSTETRICS

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COAGULATION DEFECTS IN OBSTETRIC ACCIDENTS AND DISORDERS

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IT HAS been known for many years that the clinical picture of prepartal abruption of the placenta, as well as of eclampsia, may at times include manifestations of a general hematologic disorder suggestive of purpura or hemophilia. But only since the development and use of modern hematologic methods, in particular during the past decade, has an appreciation been gained of the variety of clotting-defects underlying such hemorrhagic phenomena, and an awareness that similar defects may be encountered in other obstetric disorders. A further outcome of modern studies has been a recognition of the possibility that hematologic derangements may be present but unsuspected until major bleeding difficulties arise, or unless appropriate blood-studies are routinely employed.

COAGULATION-MECHANISM IN NORMAL PREGNANCY. To the best of the reviewer's knowledge, no women have thus far been studied at intervals throughout their pregnancies and labors with the use of hematologic techniques designed to test all the various factors currently known to be essential to the normal mechanism of coagulation. On the other hand, considerable attention has been given to the behavior of individual clotting-factors or groups of such factors[46], and an approach to the larger project has recently been made by obtaining fairly complete "coagulograms"[2] in a small group of healthy women at short intervals during late pregnancy and the course of labor[30]. The composite results of recent studies have been assembled, and are summarized in the following paragraphs.[1,6,7,8,10,12,18,19,26,36,37,38,52,66,67,75]

1. *Coagulation-time.* When the clotting-time of maternal blood is examined by the Lee-White method[33], it has been found to lie within the range of normal values during pregnancy, but tends to be shortened to the lower limits of that range during labor and the early postpartal period[6,12,30].

2. *Platelet-factors. Platelet counts*[47] obtained during pregnancy are considered to be within normal limits by

most investigators[12,30,74]. There appears to be a tendency for such counts to fall slightly in some women at the end of pregnancy and in the early stages of labor[30,74]. But there is a general and significant rise that begins toward the end of labor and continues through the ensuing postpartal period[6,30,67]. This rise approximates or exceeds maximal normal values, and includes increases in the relative number of *adhesive platelets*[52,75]. It is accompanied by increases in the speed and degree of *in vitro clot-retraction*[22,30], and in the *consumption of prothrombin*[30,43]. The magnitude of all these postpartal increases, however, is of such a limited order as to leave in doubt the question of whether the observed fluctuations reflect a specific mobilization of circulating platelets, or merely the effects of the hemoconcentration of maternal blood which normally occurs during this period.

3. *Plasma-factors.* The levels of *plasma fibrinogen* in maternal blood rise progressively throughout the course of pregnancy[19], exceeding the upper limits of normal from the sixth month onward[12,18,19]. This rise is further enhanced during the early days of the puerperium[30]. In a number of women the continuity of the rise may be interrupted during labor, at which time significant temporary drops can be found[30]. In this connection, it is of interest that a fibrinolytic mechanism has been shown to be slightly, but significantly activated in maternal blood during the same period[35].

The rise in the plasma-fibrinogen which occurs during pregnancy is accompanied by a similar, but less marked elevation in *prothrombin*[21,38,66], maximal values being attained at term. But whereas the concentration of plasma-fibrinogen continues to rise in the puerperium, prothrombin values gradually fall after the fifth day[38]. There is also evidence on record to indicate that these rises in prothrombin are temporarily interrupted by a slight fall which takes place just prior to and during labor[30,38].

Few data are available concerning the *accelerator-globulin* of maternal blood. Results obtained with the use of Stefanini's method[61] in one small group of women revealed no significant deviations from normal values during pregnancy[30].

COAGULATION-DEFECTS AND OBSTETRIC DISORDERS. For purposes of exposition, it would appear desirable to consider clotting-defects associated with obstetric disorders in the order of the frequency with which such associations have been encountered and investigated. This plan has been adopted in the following sections.

ABRUPTION OF THE PLACENTA IN LATE PREGNANCY. More than 50 years ago DeLee[14] noted that the clotting-time of the blood was prolonged in certain pregnant women in whom the placenta had become prematurely detached. In 1912, Couvelaire[11] reported a case of serious retroplacental hemorrhage in which the uterine musculature and broad ligaments were extensively infiltrated with blood, and in the same year Bar coined the term "uteroplacental apoplexy" to describe this condition. Willson[73], in reviewing 69 cases of "Couvelaire uterus" recorded in the literature prior to 1922, expressed the belief that a placental hemorrhagin was responsible for both the subplacental hemorrhage and the general hemorrhagic diathesis. Kellogg[29] later confirmed DeLee's observations concerning prolongation of the clotting-time of maternal blood in placental abruption, and Dieckmann[13] further noted subnormal levels of maternal plasma-fibrinogen.

Inasmuch as placental abruption occurs about once in every 200 pregnan-

cies, it is not an uncommon obstetric disorder. In a variable percentage of cases, the disorder is complicated by coincidental symptoms of eclamptogenic toxemia; there may be an associated anuria of toxemia or of profound shock. The condition is responsible for a substantial number of the fetal and maternal deaths encountered in modern practice[65]. It has, therefore, been investigated intensively in recent years, and hematologic data have now been accumulated among upwards of 100 patients.

The available data may be summarized as follows: Deficiencies have been noted at various times in respect to one or another of all the indices comprising a "coagulogram." The most constant and notable deficiency, however, has been fibrinogenopenia (hypofibrinogenemia)[13,23,25,27,34,55,68,69,72]. This has been closely associated with moderate reductions of prothrombin[25,27,34,55,69,72] and accelerator-globulin[27]. Thrombocytopenia has been observed in only one small group of cases[25]. Clot-resolution has been frequently noted[68,69,72]; but evidence that this or other clotting-defects may be due to the presence of a fibrinolysin has not been demonstrated with the use of reliable methods except in a few instances[69,70].

The significance of these data in relation to the problem of abruption has been illuminated considerably by the recent findings of Jackson *et al.*[25] in a careful study of 13 cases. In none of Jackson's patients was the placental accident complicated by the coincidental presence of significant manifestations of eclamptogenic toxemia. In most of the patients, opportunity was afforded (and seized) to conduct hematologic studies at an early point following the onset of the abruption. Thus, the initial data in all but 3 patients were obtained prior to the appearance of significant signs of shock, or to the use of transfusions. Under these circumstances, evidence of clotting-defects was found in 7 of the 13 patients. Early overt purpuric symptoms were also present in 3 of these 7 women. With one exception, the same 7 women eventually developed the most serious uterine hemorrhages encountered in the group as a whole. It must be noted that 5 of these 7 patients were Negro women; in such women, obstetric accidents of all types are likely to be both frequent and severe. With this reservation, the experience of Jackson and his colleagues would suggest that the appearance of a clotting-defect in otherwise uncomplicated placental abruption: (a) may be demonstrated in about 50% of cases shortly after the onset of the abruption, and that it (b) may presage the development of major hemorrhagic difficulties.

Once the clotting-defect in abruption has appeared, a tendency for it to persist, and to provoke increasing clinical difficulties, remains for as long as the fetus and placenta are retained *in utero*[53,58,59]. In the presence of such a defect, therefore, a fundamental objective of the management of abruption is to bring about the delivery of the patient without undue delay[28,53,63], by whatever obstetric measures appear to be appropriate under the circumstances. Simultaneously, the symptomatic management of any attending hemorrhagic shock, and of the coagulation-defect itself, demands the liberal use of transfusions of whole blood, and when available, of solutions of fibrinogen.* Reid and his colleagues[69,72] have furnished impressive evidence of the value of adequate amounts of infused fibrino-

*Uncontrollable postpartal uterine hemorrhage of the atonic type may occur in some cases. Such an emergency may be an indication of the presence of extensive myometrial damage of the kind described by Couvelaire, and may require that an immediate hysterectomy be done.

ogen for raising the concentration of this substance in the blood, and for arresting bleeding tendencies both prior to and following delivery. The administration of fibrinogen, therefore, would appear to be strongly indicated for combatting the clotting-defect in abruption, and particularly as a preliminary to any contemplated obstetric surgery.

Following delivery and adequate postpartal treatment of the symptomatic kind noted above, improvement in both the clinical condition of the patient and in the status of her coagulation-defect may be rapid. Surviving patients exhibit no persisting disorders of clotting function.

ECLAMPSIA. Although convulsive toxemia of pregnancy is seldom encountered in modern obstetric practice, its clinical and pathologic features are well known, and need not be commented upon here except as follows: In the most severe cases acute renal failure is generally present or impending. There is also apt to be evidence of active intravascular hemolysis[12,31,42]. In a variable percentage of cases, there will be bleeding from the gums, or hemorrhages into the brain and other vital organs[4,12,42]. Dieckmann has estimated that one woman among every six who die in eclampsia succumbs directly to the effects of cerebral hemorrhage[12].

Stahnke[60], in 1922, was probably the first to investigate the clotting functions of the blood in "eclamptic" women. His studies were confined to examinations of platelet-counts. He found such counts to be markedly lowered among those women in whom the eclamptic symptoms were severe. His observations, however, attracted little attention, for only in the past decade have additional studies of a similar nature been undertaken. The total number of cases of eclampsia and pre-clampsia investigated in this manner now exceeds 50[3,4,31,42,60].

The hematologic data currently available may be summarized as follows: The significant findings include positive tourniquet tests; prolonged clotting-times and bleeding-times; thrombocytopenia; delays in oil-clot retraction, and in prothrombin-consumption; and hemoglobinuria and hemoglobinemia[3,4,31,42,60]. The bone-marrow is usually found to be normal or hyperplastic[3,4]. In cases uncomplicated by coincidental placental abruption or fetal death, plasma-fibrinogen, accelerator-globulin and prothrombin are little, if at all, affected[3,4,42]. In short, the principal findings are likely to be: (a) those involving the number and functional status of the circulating blood-platelets, and (b) those indicative of active intravascular hemolysis.

The probable correlations between these hematologic abnormalities and the clinical phenomena of toxemia would appear to be as follows: With few exceptions, disorders of clotting function are to be found only in eclampsia itself, or in the severer forms of pre-eclampsia[3,4,67]. Encompassed in this association is a fairly constant combination comprising, on the one hand, the triad of prolonged clotting-time, thrombocytopenia and hemoglobinemia, and on the other, the syndrome of acute renal failure[3,4,42]. Overt clinical purpura or hemorragic phenomena are seen in only a minority of the patients exhibiting hematologic derangements[3,4]. The latter, moreover, may be quite transient in nature, disappearing rapidly if the eclamptic symptoms, in particular the oliguria or anuria, are promptly relieved; as can be the case if a complete renal "shut-down" has not been present too long before appropriate therapy is employed[3,4,42].

RETENTION OF DEAD FETUS IN UTERO. When a pregnant woman in whom the fetus has died and been retained *in utero* over a prolonged period eventually falls into labor, the delivery may be followed by uterine bleeding, the cutstanding feature of which is incoagulability of the blood. To date, this phenomenon has been investigated from the hematologic standpoint in 16 patients[24,25,41,44,50,70].

Clinically, the condition was formerly believed to occur only among mothers sensitized to an Rh-positive blood factor. This is no longer thought to be a necessary pre-condition[25,50]. That the associated bleeding-defect is not merely a manifestation of hemorrhagic shock is suggested by the observation that purpuric symptoms may appear prior to the onset of labor[44,50]. In a few instances, these symptoms may be attended by premature detachment of the placenta[63].

The hematologic findings that have been reported in these cases indicate that deficiencies may be present in both the platelets[24,50,70] and the plasma-factors concerned with coagulation of blood. As is the case in placental abruption, however, the principal defects appear to involve plasma-fibrinogen and its associated plasma-factors[24,25,41,44,50,70]. The administration of fibrinogen has been shown to be of therapeutic value[50].

AMNIOTIC EMBOLISM. According to Steiner and Lushbaugh[62], death in obstetric shock may occasionally be due to widespread embolization of the maternal pulmonary arterioles by amniotic debris, accidentally forced into the circulation during labor via the subplacental decidual sinuses. In such cases, shock usually develops rapidly and inexplicably, and death may be attended by manifestations of acute cor pulmonale. The diagnosis can be established with certainty only on the basis of postmortem findings.

Steiner and Lushbaugh's original description of this syndrome was published in 1941, and was based upon a postmortem study of 8 cases. Since that time, additional cases of a similar nature have been reported, and the clinical phenomena have been more fully defined and amplified[17,20,25,45,48,49,71]. Notable among these phenomena has been the incoagulability of the maternal blood in many of the cases[17], or the weakness and resolubility of such clots as may be found in blood specimens drawn during life.

Owing to the rarity of amniotic embolism, and the rapidity with which death may occur in this condition, opportunities for conducting hematologic studies on living patients have been limited. The available information, therefore, is comprised of data obtained in only 8 patients[25,45,48,49]. Plasma-fibrinogen levels have been noted to be low[25,45,48,49], and the presence of an active fibrinolysin has been claimed[45,48]. Ratnoff and Vosburgh[45], however, demonstrated the presence of a thrombin-inhibitor; they believe this inhibitor to be responsible, in part, for the failure of coagulation.

ABORTION. Clotting defects in abortion have been investigated only in recent years. In the few cases that have been studied, the abortion had been criminally induced, or attempts at induction had been made. In consequence, the symptoms included evidences of local tissue damage (either traumatic or chemical) or of sepsis, and these varied from case to case. All patients died.

The hematologic data available were obtained in 5 patients only[9,25,30,51]. All of the cases were found to have fibrinogenopenia and thrombocytopenia. An active anticoagulant was also found in one patient[9]. Fibrinolysis was investi-

gated in 3 of the patients, but its presence demonstrated in only one[9].

Discussion. The hematologic disorders here under consideration will not be confused with such conditions as chronic idiopathic purpura, parahemophilia, hemolytic anemia or the leukemias. Although the latter conditions are also occasionally seen in pregnant women, the problems involved in their recognition and management bear no resemblance to those outlined in the foregoing sections of this review. The clotting-defects described have been recorded in the literature solely as phenomena associated with certain characteristically "obstetric" (as distinguished from medical or surgical) disorders of pregnancy. The question of their relation to pregnancy itself is therefore posed.

1. FIBRINOGENOPENIA. Available evidence indicates that among the clotting-disorders associated with fibrinogenopenia, pregnancy itself may, in many instances, be the factor principally responsible for the defect. As an isolated phenomenon, fibrinogenopenia can conceivably be brought about by: (a) excessive defibrination of circulating blood as a result of disseminated intravascular clotting, (b) active fibrinolysis, or (c) a combination of these two mechanisms.

The fibrinogenopenia seen in placental abruption, retained dead fetus, amniotic embolism and abortion is currently believed to be due primarily to defibrination. The latter, in turn, is attributed to widespread miliary intravascular coagulation, following the passage of thromboplastic agents into the maternal circulation from a point of origin in the contents of the uterus[53,54,56]. The evidence supporting this concept is fourfold: (a) the demonstration of rich amounts of thromboplastic substance in human ovular and decidual tissues[32,57], (b) the postmortem finding of fibrin-clots in the smaller vessels of various organs[55], (c) the successful defibrination of the blood of experimental animals following infusion of thromboplastic material[39,40,55], and (d) the absence, on clinical hematologic study, of fibrinolytic or other mechanisms active enough to account for the observed fibrinogenopenia[53]. So far as is at present known, such active defibrination of the circulating blood is, apparently, in all fields of medicine, unique to pregnancy[53].

That fibrinolysis may be a contributory, or even alternative, factor in the fibrinogenopenias of the four obstetric conditions noted above is perhaps true only for amniotic embolism. In this condition, there is convincing evidence of the presence, not only of active fibrinolysis[34,45], but also of a heparin-like antithrombin[45,53]. Equally persuasive evidence of fibrinolysis in the remaining conditions is available for only a few cases of abortion and placental abruption. The significance of fibrinolysis in those cases in which it is found, including amniotic embolism, is as yet undefined. Several explanations are possible, but in the light of observations made in other fields of medicine, there is a strong likelihood that it is a phenomenon of shock, toxemia or sepsis[64].

2. THROMBOCYTOPENIA. Although thrombocytopenia has been found to be present, together with fibrinogenopenia, in septic abortions and some placental abruptions, the obstetric condition in which it is characteristically seen as the sole or principal factor in a clotting-defect is eclampsia. Reference has already been made to its close association with intravascular hemolysis and renal failure in that condition. Also noted previously has been the observation that overt hemorrhagic symptoms of a major nature are encountered in only a minority of eclamp-

tic patients exhibiting thrombocytopenia.

Beltz[5] and Doencke[15,16], in separate and little-known contributions to the German literature more than a generation ago, reported that they had found thrombocytopenia and hemolysis in a number of cases of chronic nephritis during the stage of renal failure. The syndrome as described by them resembles quite closely that which has only recently been noted in eclampsia.

In the light of these similarities, it is difficult to believe that the thrombocytopenia seen in eclampsia represents a phenomenon unique to pregnancy. On the contrary, the likelihood appears strong that the thrombocytopenia observed not only in eclampsia, but also in abortion and placental abruption, is akin to that described by Beltz and Doencke in nephritis. The common denominator would appear to be renal failure, whether from nephritis or from the more acute anoxial insults associated with shock, toxemia and other grave accidents.

Summary. The results of recent hematologic studies of coagulation-defects encountered in such obstetric conditions as prepartal abruption of the placenta, eclampsia, prolonged retention of a dead fetus *in utero*, amniotic embolism, and septic abortion have been briefly reviewed.

The observed defects have been found to involve abnormalities of both the plasma and platelet-factors of the blood. The degree to which each of these factors may be affected varies considerably among the obstetric disorders studied. Thus, in eclampsia the principal defect concerns the platelet factors, whereas in the remaining disorders the outstanding abnormalities involve plasma factors, with or without associated deficiencies of platelet function.

The relations of these defects to the clinical phenomena of the obstetric conditions with which they are associated has been examined. Although a hemorrhagic diathesis is mainly latent in some disorders, the threat of overt hemorrhagic difficulties is ever present in all, manifesting itself most frequently and seriously in placental abruption. From the clinical standpoint, the diatheses as a group are closely related to the state of pregnancy, in that they are usually amenable to reversal with the termination of pregnancy in patients not too gravely ill from shock or complications when first seen. Treatment may, therefore, be successful quite independently of the treatment of the coagulation-defect. The fibrinogenopenic disorders are readily combatted with the use of infusions of fibrinogen, except in amniotic embolism. Such infusions have been shown to be of signal value in placental abruption.

In attempting to appraise the general pathologic significance of these coagulation-defects, it is possible that some of the fibrinogenopenias observed are unique to pregnancy, whereas the remaining fibrinogenopenias and the thrombocytopenias may reflect derangements which obstetric shock, toxemia or sepsis share in common with comparably grave disorders in medicine and surgery.

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PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF JANUARY 18, 1955

INFORMAL SEMINAR ON SOME ASPECTS OF THE PHYSIOLOGY OF THE ERYTHROCYTE

Introductory Remarks. L. M. TOCANTINS, M.D. (Department of Medicine, Jefferson Medical College)

Osmotic Hemolysis and Permeability Measurements. M. H. JACOBS, PH.D. (Department of Physiology, University of Pennsylvania). The mammalian erythrocyte presents several special advantages for the quantitative measurement of cell permeability. Two of the most important are the virtual constancy of its surface area throughout a wide range of osmotic volume changes and its extremely high permeability to water. Because of the latter the entrance of all but the most rapidly penetrating solutes takes place under conditions of approximate osmotic balance, and the relation between the volume of the cell water and the amount of a solute that has entered it assumes a simple form. Furthermore, a relation also exists between cell volume and hemolysis, the rate of attainment of which can be measured with ease and accuracy. In attempting to find this relation it was discovered that a fundamental error results when inferences as to the normal osmotic properties of erythrocytes are drawn from their behavior in "fragility" determinations with hypotonic sodium chloride solutions. In such solutions at least 3 mechanisms of swelling and hemolysis can be distinguished. The first is the primary osmotic entrance of water into the unaltered cell, which is virtually complete in a few seconds. It is best seen in non-hemolytic hypotonic salt solutions and frequently even in hemolytic glucose solutions. The second, which is much more prolonged, is associated with ionic exchanges, probably chiefly bicarbonate ions from the cell for chloride ions from the solution, since it can be prevented by the presence of bicarbonate in the hypotonic solution. Finally, there is reason to believe that excessively swollen cells may become abnormally permeable to cations and undergo still further swelling and hemolysis through the operation of the Donnan principle. Progress has been made in the development of methods for separating the primary normal osmotic effects from the secondary, more or less abnormal ones.

Measurement of the Life Span of Erythrocytes. MAX M. STRUMIA, M.D. (Department of Pathology, Bryn Mawr Hospital). The measure of life span of erythrocytes is an essential procedure in the Laboratory of Clinical Pathology because: (1) expansion of blood transfusion has brought about the realization that *in vitro* tests of viability, such as the osmotic resistance, are at best a screening process; (2) ever-increasing evidence has established that accelerated hemolysis plays a major part in many forms of anemias previously considered due entirely to altered erythropoiesis.

By life span of erythrocytes is meant here the average length of time during

which an erythrocyte remains in circulation. Part of this life, probably a matter of 1 or 2 days, is in the form of reticulocytes.

Direct methods of measure of red cell life span include tagging with radioactive isotopes (Fe^{55}, Fe^{59}, Cr^{51}, C^{14}) or with the stable isotope N^{15}. The mean life of red cells in man with the N^{15} method has been established at 120 to 128 days.

Results similar to isotope tagging have been obtained by serological differentiation of non-agglutinable cells (so-called Ashby method) generally by transfusing an A patient with O group blood.

An indirect method of measuring the life span is based on the measure of the total urobilinogen excreted in relation to the total mass of circulating red cells. Although much less precise than the method previously mentioned, this method gives valuable clinical information.

The Relation of Erythrocytes and Platelets to a Sphering System of Plasma Origin. A. S. HAMILTON, M.D., AND I. S. RAVDIN, M.D. (Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania). Previously published evidence demonstrated that contact with plasma during storage contributed to the deterioration of canine erythrocytes (**Hamilton,** Surg. Forum, Proc. 36th Clin. Congress, Am. Coll. of Surgeons, 1950). When successive transfusions of erythrocytes from the same donor were tested by the Ashby method in the same recipient, the survival of a preparation of washed erythrocytes stored in albumin-glucose-saline solution for 60 days compared favorably with that of the erythrocytes stored as ACD blood at 4 to 7° C. for 21 days.

Development of a biological method for assaying the activity of the cell-injuring factor from plasma permitted more detailed studies. The primary lesion produced in fresh erythrocytes by the active agent involved the immediate transformation of biconcave disks to crenated spherocytes; hemolysis *in vitro* was a secondary effect when it occurred. Fresh mixed cell-populations were heterogeneous in their resistances to the sphering agent, reticulocytes being among the most resistant cells.

Fresh plasma or serum of humans, dogs, and rabbits contained low levels of sphering agent which was inhibited by heat-sensitive factors at an equilibrium below the thresholds of fresh erythrocytes. By enzymatic action cell-free plasma developed sphering activity within a few hours at room temperature. This reaction proceeded slowly at 0 to 7° C. and was markedly inhibited by storage of plasma in the frozen state at minus 15° C. A lowering of cell-threshold during storage intensified response of such cells to low sphering activity.

The presence of erythrocytes or platelets in plasma during storage at room temperature reduced its sphering activity. The preformed sphering agent was successfully absorbed or inactivated by brief contact with adequate numbers of washed erythrocytes.

Following the transfusion of aliquots of 6-day-old non-sphered and experimentally sphered erythrocytes from the same blood collection into paired canine recipients, 91% of the non-sphered, and 63% of the sphered cells survived at 7 days post-transfusion. The elimination of the previously sphered cells was complete by 64 days post-transfusion.

Transfusion of Erythrocyte-Glycerol Mixtures After Storage at Low Temperatures. H. A. SLOVITER, PH.D., M.D., AND RITA M. TIETZE (Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania). It has been demonstrated that the via-

bility of erythrocytes in a glycerol medium can be successfully preserved for several months at temperatures well below freezing (Lancet, **2**, 501, 1952). These hypertonic cells cannot be transfused directly, and so it was thought necessary to remove all the glycerol prior to transfusion. No simple and satisfactory method for doing this has been available. The following relatively simple procedure which does not require the removal of glycerol is proposed. To the thawed erythrocyte-glycerol mixture is added one-half its volume of 50% glucose in 0.9% sodium chloride solution. The glucose does not penetrate the cells appreciably and serves to balance the osmotic pressure due to glycerol inside the cells. The resulting mixture is then diluted with twice its volume of 0.9% sodium chloride solution. This dilute suspension of red cells can be transfused directly or a higher hematocrit product can be obtained by a centrifuging and resuspension operation. The ability of these red cell suspensions satisfactorily to withstand the osmotic effects of transfusion has been shown by *in vitro* experiments in which a stirred large volume of plasma served to simulate the plasma volume of a recipient. The initial results of a study now in progress indicate that red cells stored and prepared for transfusion in this manner have a satisfactory post-transfusion survival. No undesirable effects have resulted from the infusion of the glycerol contained in the red cell suspensions. (Supported by a grant from National Heart Institute, National Institutes of Health, U. S. Public Health Service.)

BOOK REVIEWS AND NOTICES

CONGENITAL SYPHILIS. By DAVID NABARRO, M.D., F.R.C.P., Consulting Pathologist, Hospital for Sick Children, London. Pp. 470; 95 ills. London: Edward Arnold, Ltd., 1954. (Williams & Wilkins Co., Baltimore, U. S. Agents.) Price, $10.00.

THIS comprehensive treatise is based on the author's extensive experience at a special clinic for children in Britain. More than 900 cases of congenital syphilis were studied during the period 1916 to 1939, when the clinic was closed because of World War II. This book, therefore, is an historical record of congenital syphilis as seen in Britain in the pre-penicillin era. Although the prevalence and intensity of the disease has greatly diminished in recent years in Britain, the United States of America, and other equally fortunate countries, there are many parts of the world where congenital syphilis is still an important problem. All physicians, however, regardless of geographic location, will find this volume an interesting and valuable reference on every aspect of congenital syphilis. C. Z.

ANATOMY: REGIONAL AND APPLIED. By R. J. LAST, M.B., B.S., F.R.C.S., Professor of Applied Anatomy, Royal College of Surgeons of England. Pp. 665; 309 ills., many in color. Boston: Little, Brown and Company, 1954. Price $10.00.

THE author of this volume is Examiner in Anatomy for the Primary Fellowship Examination of the Royal College of Surgeons of England, and the work is an outgrowth of his postgraduate lectures, emphasis being placed on practical considerations. In this connection, the subject matter is treated from the viewpoints of embryology, phylogeny, and physiology, each region being so covered

The book is cleverly written and e[illegible]asis is placed on applied principles; at several points unimportant details are labeled unimportant (namely, p. 270). It contains numerous illustrations from the Museum of the Royal College of Surgeons of England, plus drawings by the author. There are many anatomic memory couplets; for example, "The formula 'PAD and DAB' indicates that palmar adduct and dorsal abduct the fingers," (p. 123); or "There is a point to be noted at each of the even-numbered ribs" (p. 262). An especially practical passage details the embryological development of the gut (p. 294).

This book provides a useful guide for postgraduate anatomy students and board candidates. B. B.

TEXTBOOK OF OPERATIVE GYNAECOLOGY. By WILFRED SHAW, M.A. (CAMB.), M.D., F.R.C.S. (ENG.), F.R.C.O.G., Late Surgeon in Charge, Gynaecological and Obstetrical Department, St. Bartholomew's Hospital. Pp. 444; 382 ills. London: E. & S. Livingstone, Ltd., 1954. (Williams & Wilkins Co., Baltimore, U. S. Agents.) Price, $19.00.

THIS textbook was prepared by Wilfred Shaw to record the operative techniques used in the Gynaecologic Department of St. Bartholomew's Hospital. Unfortunately, Shaw died before the book was compiled, but he did finish the entire text himself; his colleagues and the publishers correlated the manuscript and the illustrations.

The book is divided into 29 chapters, the first of which are devoted to a discussion of preoperative preparation, instruments, anesthesia, general technique, postoperative care and anatomy. The remaining material is considered in the usual manner; at the beginning of each chapter indications for the operative procedures to be described and in some instances pathologic changes which may be encountered are presented.

The space allotted to the various procedures and the detail with which they are described is not always determined by the relative importance of the topic. For instance, the operative treatment of sterility is covered in 6 pages, half of which are devoted to diagnostic tests. Salpingostomy is well described but not illustrated; the only illustrations being for ovarian implantation procedures. The treatment of stress urinary incontinence is covered in 12 pages with only one-half page being devoted to vaginal procedures and the rest to the sling methods. Six types of suspension operation and ventrafixation are described for the correction of retroversion.

The sections on vaginal surgical procedures for the repair of relaxations, fistulas and congenital defects are excellent, as are those concerning the correction of operative injuries to the bowel and urinary tract. The illustra-

tions for these sections are particularly good.

The text is easily read and is interesting and the illustrations are of good quality but in many instances there are too few. Only a few references are given and for the most part they are not well selected, being old and outmoded.

This book should be of value to the specialist in gynecologic surgery primarily because of the excellence of the sections on vaginal operations. The other procedures illustrated and described differ little from those in similar books. J. W.

FAT METABOLISM. Edited by VICTOR A. NAJJAR, Johns Hopkins University School of Medicine. Pp. 185; 43 ills. Baltimore: The Johns Hopkins Press, 1954. Price, $4.50

THIS is an outstanding symposium on fat metabolism numbering among the contributors, like its predecessor on carbohydrate metabolism, many of the leading clinical and laboratory investigators to be found in the field in this country. The problem of obesity is presented in a refreshing fashion in a series of four papers. One of these by Mayer illuminates to a degree our lack of knowledge concerning the basic physiologic and metabolic alterations in clinical and experimental obesity; further data on his glucostatic mechanism of regulation of food intake are reported. Both Mayer and Wilkins propose that study of the decreased expenditure of energy as an etiologic factor in obesity be pursued. Fundamental work on the metabolism of fat, of the role of coenzyme A and of the action of heparin and clearing factor in lipid transport is reviewed by Lipmann, Lehninger, Gurin, Kornberg and Anfinsen. Various aspects of fat metabolism in relationship to diabetes mellitus and atherosclerosis are included in this remarkable volume. It serves well to bring to the clinical investigator the recent biochemical advances and to the biochemist the clinical problems which are the stimulus for basic research. C. S.

PROCEEDINGS OF THE SECOND NATIONAL CANCER CONFERENCE, 1952, Two volumes. Pp. 1,687. New York: The American Cancer Society, Inc., 1954. Price, $7.50 per set.

THE Second National Cancer Conference, held in Cincinnati in 1952, was sponsored by the American Cancer Society, Inc., the National Cancer Institute, and the American Association for Cancer Research. All but 145 pages consist of the records of the proceedings of the fourteen special panels including breast, genitourinary, head, and neck, lymphoma-leukemia, female genital tract, gastrointestinal, lung, radio-biology, genetics, cytology, chemotherapy, virology, steroids, and isotopes.

The participants of a conference of such magnitude included, as one would expect, most of the nation's authorities and a few from abroad. The two volumes contain a great deal of worthwhile and important material, but like most published conference reports, it is of value only in reading the whole and not as a reference. Reading the whole, on the other hand, is a tedious business however, because the average clinician will probably find a vast amount of material which is not designed for his particular interest. E. A.

YEAR BOOK OF MEDICINE (1954–1955 SERIES). Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., FRANZ J. INGELFINGER, M.D., AND PHILIP K. BONDY, M.D. Pp. 711; 115 ills. Chicago: Year Book Publishers, Inc., 1954. Price, $6.00.

THE latest volume of this series contains abstracts of articles published between May, 1953, and May, 1954. The format is the same as that of its predecessors with sections devoted to 1) Infection, 2) The Chest, 3) The Blood and Blood-Forming Organs, 4) The Heart and Blood Vessels and Kidney, 5) The Digestive System, and 6) Metabolism. The respective section editors have again prepared concise, pertinent summaries of numerous articles, with surprisingly few omissions.

The present volume will be helpful to anyone attempting to keep up with the rapid progress being made in internal medicine. C. Z.

SURGICAL TREATMENT OF CANCER OF THE CERVIX. Edited by JOE V. MEIGS, M.D., Clinical Professor of Gynecology, Harvard Medical School. Pp. 462; 209 ills. New York: Grune & Stratton, Inc., 1954. Price, $12.00.

THIS volume on Surgical Treatment of Cancer of the Cervix was prepared to record the various operations which are currently being used to treat this condition. Until Meigs, the editor, revived interest in radical pelvic dissection the standard treatment for many years had been Roentgen-ray and radium irradiation. Since his initial reports more

and more women with cervical malignancy are being operated upon. As stated in the preface: "It is the editor's hope that this volume will give the surgeon or gynecologist who wishes to perform these operations an idea of the meticulous care needed before, during and after surgery."

The introduction provides a general survey of the problem. The historical background of operative therapy is presented and the reasons why operation is preferable to irradiation are discussed. The clinical classification of cervical carcinoma is described and compared with a surgical and pathologic classification suggested by Meigs and Brunschwig.

Twenty-three surgeons and gynecologists, each of whom is a specialist in some phase of the surgical treatment of cervical cancer, were selected as contributors. Various operations, such as radical hysterectomy with pelvic lymph node dissection, radical vaginal hysterectomy, total pelvic exenteration and others, are described. For most procedures the methods of at least 2 different surgeons are presented. Pelvic anatomy, the methods by which cancer is disseminated from the cervix and some of the complications of surgical treatment are also discussed.

The text has been well coordinated and there is little reduplication of material. The illustrations are good and well placed with regard to the text with the exception of two articles which are illustrated by photographs in which the details are often not clear.

This volume should prove to be valuable as a reference for the relatively few individuals who should be performing the operative procedures described. J. W.

THE AUXILIARY HEART. By WILLIAM WALTER WASSON, M.D., Consulting Radiologist, St. Anthony, Children's and St. Luke's Hospitals, Denver. Pp. 184; 72 ills. Springfield, Ill.: Charles C Thomas, 1954. Price, $10.50.

THIS is a detailed presentation of the anatomy, physiology and physiodynamics of the chest that pertain to the auxiliary heart, to the right side of the heart proper, with a discussion of the pathologic conditions that influence the actions of the auxiliary heart, particularly concerning the respiration. Conditions of the chest that interfere with the proper respiratory function, or that represent a reversal to the fetal state, create a strain on the right heart. Evaluation of the roentgenogram of the chest permits to relate the air content of the lungs to the anatomical structures and the pulmonary circulation. A special chapter is devoted to the diaphragmatic syndrome comprising a group of symptoms in which the improper functioning of the diaphragm is the chief causative factor. A chapter dealing with the history of the lesser circulation, by M. W. Stein, makes most interesting reading. Clinical applications of the deductions obtained are ample. An extensive and carefully chosen bibliography will be of great value to the student in this field. This is a splendid, well correlated study that should be of interest and help to surgeons, clinicians, radiologists and physiologists. H. R.

NEW EDITIONS

Actions of Radiations on Living Cells. By The Late D. E. LEA. 2nd ed. Pp. 416; 61 ills. New York: Cambridge University Press, 1954. Price, $6.00.

THE second edition of this highly authoritative work contains extensive corrections and revisions which the late author had left among his papers. Additional material supplied by current discoveries has also been incorporated into the text by Dr. L. H. Gray. The present volume, therefore, is an up-to-date version of a book which is considered by many to be a masterpiece in its field.

Relevant physical properties and chemical effects of ionizing radiations are first discussed. Succeeding chapters deal with the effects of radiations on viruses and on the genes and chromosomes of higher cells. The killing of cells by radiation is considered in the last chapter.

Investigators in related fields of medicine, genetics, biology, and biophysics will find much of value in this book. C. Z.

Cleft Palate and Speech. By MURIEL E. MORLEY, B.Sc., F.C.S.T., Speech Therapist to the Royal Victoria Infirmary, The Hospital for Sick Children, and The Newcastle General Hospital, Newcastle-upon-Tyne. 3rd ed. Pp. 173; 64 ills., Edinburgh and London: E. & S. Livingstone, Ltd., 1954 (Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $4.25.

MISS MORLEY is Speech Therapist to the Royal Victoria Infirmary, The Hospital for Sick Children, and The Newcastle General Hospital. The present work, the third edition, has been revised by her. In the preface to the first edition, Miss Morley states that "the greater part of this work was originally approved by the British Society of Speech Therapists, now the College of Speech Therapists, as a thesis for the Diploma of Membership of that society." Although the book consists of only 173 pages and contains 64 illustrations, there is a wealth of clear, concise information which should delight anyone

interested in the problem. The author's discussions concerning the mechanism of speech and the reasons for success or failure of certain surgical techniques demonstrate clearly her insight into this condition, which affects about one of every 1000 infants. G. R.

Essentials of Medicine. The Art and Science of Medical Nursing. By Charles Phillips Emerson, Jr., A.B., M.D., Associate Professor of Medicine, Boston University School of Medicine, and Jane Sherburn Bragdon, R.N., B.S., Associate Director, School of Nursing, Massachusetts Memorial Hospitals. 17th ed. Pp. 922; 268 ills., 19 in color. Philadelphia: J. B. Lippincott Co., 1955. Price, $4.75.

This book should undoubtedly prove valuable to the student nurse for it covers the field comprehensively. The orientation at the beginning of each system will be most helpful in giving the nurse a preview of the subject material to be studied. The content of the book is dependable; the current therapy is carefully described. A readable explanation of the pathology and physiology of each disease with graphic description of signs, symptoms, and treatment is included. The completing of each unit with questions similar to those the student will encounter when writing her State Board Examinations is an excellent addition. R. W.

NEW BOOKS

Intern's Manual (Cook County Hospital). By Arthur Bernstein, M.D., Assistant Medical Superintendent, Cook County Hospital. Pp. 292; 13 ills. Chicago: Year Book Publishers, Inc., 1954. Price, $3.00.

This handy little book is based on the procedures followed by the interns and house staff at the Cook County Hospital in Chicago. Although methods employed in other hospitals may differ somewhat from some of those described in this volume, it should be readily adaptable and valuable for interns working in institutions which have no comparable guide to aid them. C. Z.

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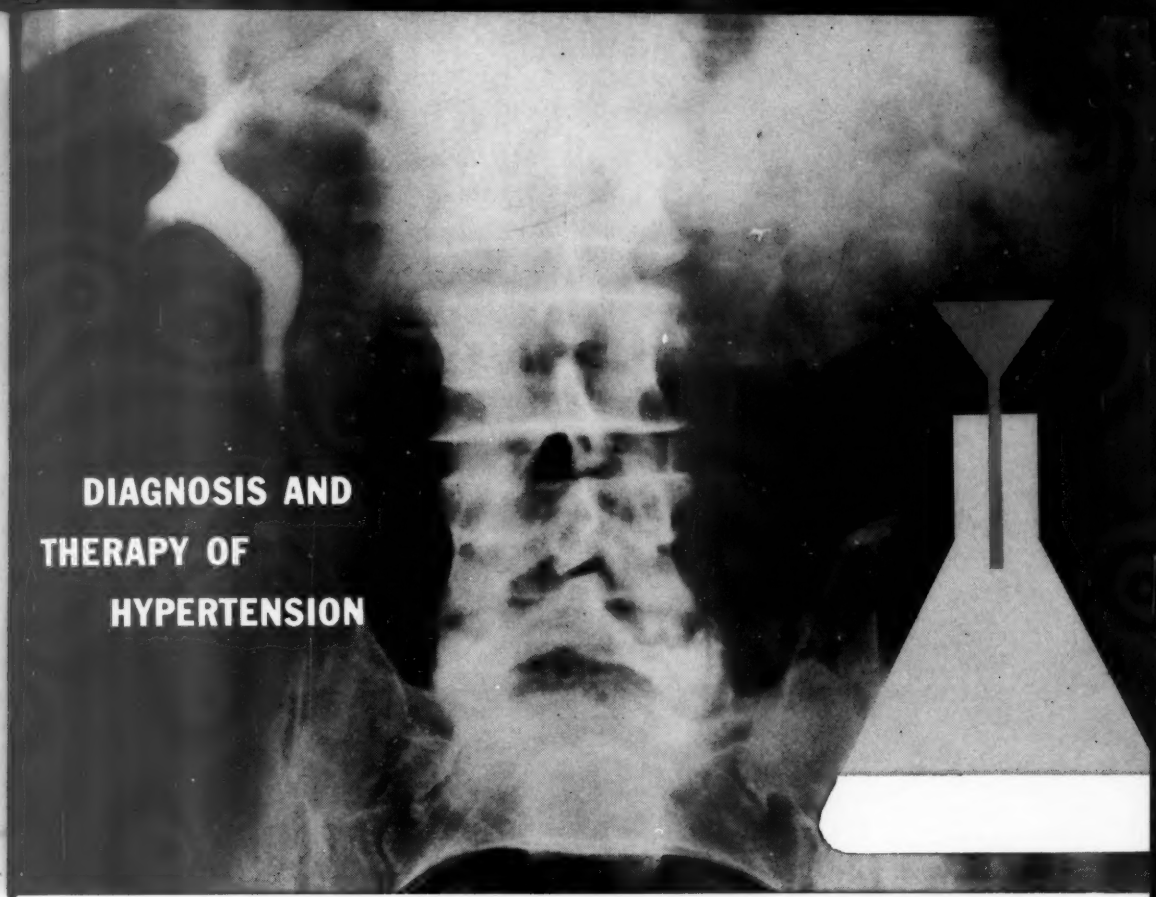

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*Dennis, E.; McConn, R. G.; Ford, R. V.; Hughes, W. M.; Beazley, H. L., and Moyer, J. H.: Postgrad. Med. *16*:300 (Oct.) 1954.

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